Chapter 7

# Mild Thyroid Deficiency in the Elderly

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## 1. Introduction

Subclinical hypothyroidism (sHT) is defined as serum thyrotropin-stimulating hormone (TSH) concentration above the statistically defined upper limit of the reference range in the face of serum free $T_4$ ($FT_4$) and free $T_3$ ($FT_3$) concentrations within the normal range (Ross, 2004). sHT is a frequent condition among the general population, especially middle-aged and elderly women (Canaris et al., 2000). Depending on the degree of TSH elevation, sHT has been associated with hyperlipidemia, intermediary metabolism alterations, arterial hypertension and cardiovascular disease (CVD) as well as neuropsychiatric features, including cognitive impairment (Ashizawa et al., 2010; Biondi & Cooper., 2008; Cappola et al., 2006; Ceresini et al., 2010; Mitrou et al., 2011; Monzani et al., 2006; Rodondi et al., 2010; Tan et al., 2008; Tappy, 1987). Interestingly, the analysis of variation in thyroid function tests in healthy volunteers has shown that the physiological individual reference ranges for test results are narrow compared with laboratory references (Andersen et al., 2002). This finding suggests that a test result within laboratory reference limits is not necessarily normal for an individual. Giving that serum TSH responds with logarithmically amplified degree to minor changes in serum $T_4$ and $T_3$, abnormal serum TSH may indicate that $T_4$ and $T_3$ are not normal for an individual although still within the laboratory references. These data point out that the distinction between subclinical and overt thyroid failure (elevated serum TSH and low $T_4$ and/or $T_3$) is somewhat arbitrary. Indeed, for the same degree of thyroid function abnormality, the diagnosis depends to a considerable extent on the position of the patient's normal set point for $T_4$ and $T_3$ within the laboratory reference range.

Because sHT is mainly detected as a biochemical TSH abnormality, the definition of the TSH reference range represents a critical point, especially in the elderly (Baloch et al., 2003; Olsen, 1978; Dayan et al., 2001). In the past, the upper normal limit of TSH was considered about 10 mIU/L with the first-generation TSH RIA assay while, the current normal reference range of serum TSH concentration is around 0.45 to 4.5 mIU/L (Biondi & Cooper, 2008; Surks et al.,

2004). Considering that serum TSH concentrations in a healthy population have a skewed distribution with a "tail" toward higher TSH values, the use of age specific reference limits for TSH has been suggested (Surks et al., 2004). This is especially proper in the elderly, in whom normal TSH is often shifted to a higher level (Mariotti, 1995) and the clinical presentation may differ from that in their younger counterparts (Mohandas, 2003). These considerations outline how making a correct diagnosis of sHT is challenging in the elderly but crucial to avoid significant misclassification of patients with abnormal TSH, who may or may not have thyroid dysfunction and may receive unnecessary or even harmful therapy (Laurberg, 2011). Indeed, the clinical significance of sHT in the elderly should be ascertained also in relation to the physiological changes of thyroid function with ageing (Biondi & Cooper, 2008; Carlè, 2007; Ceresini, 2010; Helfand, 2004; Surks et al., 2004). Therefore, the fundamental clinical question regarding these patients is on the clinical significance of sHT and the actual need of hormone replacement therapy (Villar, 2007).

## 2. Epidemiology

Several population-based studies have reported that sHT is common in the general population, with a prevalence that increases with increasing age (Gharib et al., 2005a,b; Hollowell et al., 2002; Samuels, 1998; Tunbridge et al., 1977). In interpreting epidemiologic data, it should be taken into account that the ability to identify people with sHT varies by TSH assay and cut-off value, which ranged from >3 to >7 mIU/L (Kanaya et al., 2002; Rivolta et al., 1999). In this setting, it is noteworthy that some investigators suggest that the upper limit of normal for serum TSH level should be 2.5 mIU/L (Spencer et al., 1993). In support of this position is a higher prevalence of anti-thyroid antibodies in subjects with serum TSH levels >2.5 mIU/L (Vanderpump et al., 1995). Reasoning about these considerations, it is not astonishing that the reported prevalence of sHT in the general population ranges widely from 1.3% to 21%, depending on age, gender, and iodine intake (Kanaya et al., 2002; Rivolta et al., 1999; Samuels, 1998; Sawin et al., 1985; Tunbridge et al., 1977; Wang et al., 1997).

In the Wickham survey, the prevalence of sHT (TSH > 6 mIU/L) was 7.5% in women and 2.8% in men (Wickham study). An age dependent increase in serum TSH concentrations was found only when women with high serum anti-thyroid antibody values were included in the analysis; with 17.4% prevalence of sHT in women older than 75 years (Wickham study). Accordingly, in a Dutch study the prevalence of sHT in a group of middle-aged women (mean age 55 years) was 4%, the rate rising to 7.3% 10 years later (Geul et al., 1993). The higher prevalence of sHT in older people was confirmed by data from the Framingham Study, which reported a prevalence of sHT of 8.2% in men and 16.9% in women, older than 60 years and, the Colorado study (16% in men and 21% in women older than 74 yrs) (Sawin et al., 1979, Canaris et al., 2000). Overall these findings demonstrate that ageing is associated with an increased prevalence of positive anti-thyroid antibody titers and mild hypothyroidism (Mariotti et al., 1995). The prevalence of sHT varies also according to iodine intake; being higher in areas with elevated intake with respect to areas with low-normal or deficient intake (Biondi & Cooper, 2012). In this setting, the occurrence of sHT among nursing home elderly residents was 4.2% in an iodine-deficient area (urinary iodine 72

micrograms/g creatinine), 10.4% in region of obligatory iodinated salt prophylaxis (urinary iodine 100 micrograms/g creatinine) and 23.9% in an abundant iodine intake area (urinary iodine 513 micrograms/g creatinine) (Szabolcs et al., 1997).

Overall, these data show that sHT is a very frequent condition and raise the question of the opportunity for general population screening programs, although a consensus is still lacking on this topic (Biondi & Cooper, 2012). The above notwithstanding, screening older people for thyroid disorders is still suggested by some authorities, aiming at the discovery of previously undiagnosed cases of overt hypothyroidism and the monitoring of cases with subclinical dysfunction (Ladenson et al., 2000; Surks et al., 2004).

## 3. Subclinical hypothyrodism: Clinical features and etiology

Hypothyroidism is a graded phenomenon that encompasses a wide variety of clinical conditions from full blown myxedema to sHT, which is characterized by elevated serum TSH concentrations in the face of normal free thyroid hormone levels (Cooper, 2001). Currently, the most widely accepted interpretation of these biochemical findings is that increased TSH is an indication of slightly reduced peripheral thyroid hormone effect, leading to mild hypothyroidism instead of a new steady state of euthyroidism (Karmisholt et al., 2011, Ross, 2004). In a consensus statement of the American Association of Clinical Endocrinologists, sHT was classified in two categories according to TSH level: mildly increased serum TSH levels (4.5–10 mIU/liter), and more severely increased serum TSH value (>10 mIU/liter) (Gharib et al., 2005a,b). However, this classification was not adopted in all clinical investigations, thus making the comparison of different trials quite difficult.

There is scientific consensus that sHT is caused by the same etiology of overt hypothyroidism (Biondi & Cooper, 2008), the most frequent one being Hashimoto's thyroiditis. This is an autoimmune, inflammatory disorder of the thyroid gland, whose prevalence increases with increasing age, being higher in women (Canaris et al., 2000; Surks et al., 1996). Other causes of primary hypothyroidism may result from therapies that destroy the thyroid tissue such as radioactive iodine treatment, external radiation therapy or partial thyroidectomy (Cooper, 2001). Chemotherapy also was associated to hypothyroidism in patients with cancer or lymphoma (Hancock et al., 2001; Kumar et al., 2004). Moreover, both subclinical and overt hypothyroidism could be induced by many drugs such as amiodarone, lithium carbonate, type I interferons, sulfonamides and several other toxic molecules (Basaria & Cooper, 2004; Caraccio et al., 2005).

Patients with sHT have a different rate of progression to clinically overt hypothyroidism in the presence or not of autoimmunity: 2.6% each year if thyroperoxidase (TPO) antibodies are absent and 4.3% if they are present (Vanderpump et al., 1995). However, a significant number of sHT subjects do not show progression and some experiences normalization. One of the most predictive markers of progression to overt hypothyroidism is serum TSH level higher than 10 mIU/L, by contrast a level less than 6 mIU/L depicts a lower likelihood of progression (Fatourechi, 2009). Accordingly, a clinical study, enrolling men and women older than 55 years with mean follow-up of 32 months, indicated that serum TSH levels normalized in 52% of those with serum TSH value less than 10 mIU/L (Díez & Iglesias, 2004).

The most common symptoms reported by sHT patients are the same although less evident than those observed in overt hypothyroidism: dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramp, cold intolerance, puffy eyes, constipation, and hoarseness (Canaris et al., 2000; Canaris et al., 1997). It is conceivable that clinical symptoms of hypothyroidism are related to the degree of thyroid failure, disease duration, and individual sensitivity to thyroid hormone deficiency (Biondi & Cooper, 2008). However, the presence of typical symptoms in patients with sHT remains controversial considering that many of them are non-specific and shared with many clinical conditions, especially in the elderly. Therefore, it is difficult to distinguish euthyroid subjects from sHT patients only by using clinical symptoms (Biondi & Cooper, 2008). Baseline data from a randomized clinical study confirmed a significant prevalence of hypothyroid symptoms among individuals with sHT (Cooper et al., 1984). Moreover, Canaris et al., (2000) reported fewer symptoms related to hypothyroidism in subclinical than in overt hypothyroid patients, but more frequently than in euthyroid controls. However, this study did not distinguish between treated or untreated subclinical and overt hypothyroid patients. By contrast, other cross-sectional and case-control studies did not confirm these observations, but they were conducted among selected or referred populations often involving old hospitalized patients (Bemben et al., 1994; Zulewski et al., 1997). Age represents a confounding factor that may hinder the identification of symptoms of mild hypothyroidism: the typical findings of hypothyroidism are less common in the elderly and, if present, often either resemble or are attributed to chronic illnesses, drugs, depression or ageing *per se* (Billewitc et al., 1969; Samuels, 1998). Therefore, clinical signs and symptoms are poor predictors of sHT especially in the elderly; this fact may explain why the diagnosis of sHT, and sometime overt disease yet, may be delayed in older people (Biondi & Cooper, 2008).

## 4. Thyroid function and ageing

The relationship between thyroid function and ageing has been hypothesized more than one decade ago (Mariotti et al., 1995). Human ageing is associated with an increased prevalence of serum anti-thyroid antibodies and overt or mild thyroid dysfunction (Hollowell et al., 2002; Gharib et al., 2005a,b; Samuels, 1998; Tunbridge et al., 1977). Several clinical studies confirmed an age-dependent decrease of thyroid function including iodine uptake and thyroid hormone production (Hollowell et al., 2002; Gharib et al., 2005a,b; Samuels, 1998; Sawin et al., 2009; Tunbridge et al., 1977). Although there is a consensus on the detrimental effects of overt hypothyroidism in older patients, the clinical relevance of mild to moderate thyroid failure remains an uncertain area (Surks et al., 2004) and, animal models indicated that low thyroid hormones are associated to increased life span (Ooka et al., 1983). The relative small number of epidemiological studies with inappropriate statistical power, and the lack of large prospective randomized trials directed to evaluate the therapeutic effect and impact on survival of hormonal therapy in mild thyroid impairment, does not allow to conclude whether mild thyroid impairment is a favorable phenotype or a negative clinical condition, especially in older people. An age-dependent thyroid dysfunction (particularly hypothyroidism) has been well documented in the elderly, including the oldest-old

population (>85 yr) (Helfand et al., 2004; Mariotti et al., 1993). An interesting study focused on thyroid function during physiological ageing was carried out by Mariotti et al. (1993). In this study thyroid status was assessed in 41 healthy centenarians and 33 healthy elderly subjects as compared to two control groups: 98 healthy normal adult subjects and 52 patients with miscellaneous non-thyroidal illness. Healthy centenarians showed a lower prevalence of positive anti-thyroid autoantibody titer than elderly controls with a relatively low (7%) prevalence of sHT although the median serum $FT_3$ level was lower than in each other group. Interestingly, median serum TSH level of centenarians was lower than in healthy elderly subjects, in whom however, was significantly lower than in young controls (Mariotti et al., 1993). This study did not resolve the question whether the decreased $FT_3$ and TSH value observed in healthy centenarians, represents an adaptive mechanism to reduced metabolic homeostasis or a protective condition in ageing. At partial odds with these data, a population based survey and one large cross-sectional study (Atzmon et al., 2009; Surks et al., 2007) showed a progressive shift of the normal serum TSH range towards higher values from healthy young individuals up to centenarians. Overall these data seem to suggest that ageing is associated with a certain degree of down regulation of the hypothalamus-pituitary-thyroid-peripheral axis, although the clinical significance of such condition is far to be elucidated. To this regard, Rozing et al. (2010) reported that the offspring of nonagenarian siblings presented a lower thyroidal sensitivity to TSH and a paradoxical beneficial cardiometabolic profile as compared to their partners. The authors concluded that the favorable role of low thyroid hormone metabolism on health and longevity, already observed in animal models, might be applicable to humans as well. However, the study by Rozing et al. (2010) enrolled a specific population in order to identify familial determinants of healthy longevity in nonagenarian siblings. The results might, therefore, be affected by some bias and cannot be extended to the general population. On the other hand, a cross-sectional study by Corsonello et al. (2010) carried out in 604 home-dwelling subjects born in Calabria (southern Italy), with ancestry in the region ascertained up to the grandparents, confirms a declining of serum thyroid hormone levels with ageing. Moreover, lower levels of $FT_3$, $FT_4$ and TSH were found in centenarians' children and nieces/nephews with respect to age-matched controls. Indeed, the authors conclude that an age-related subtle decline of thyroid function (either due to a familial component or due to a reset of the thyroid function occurring between the sixth and the eighth decade of life) seems to be related to longevity. Two other studies support the hypothesis that mild hypothyroidism in elderly might be associated to a better survival and performance status. In the first, Gussekloo et al. (2006) found lower all-cause and cardiovascular mortality in hypothyroid subjects aged more than 85 years followed for 4 years, when compared with euthyroid individuals. In the second, van den Beld et al. (2005) showed that low-serum $T_3$ (with normal $rT_3$) concentrations were associated with a better survival and physical performance, while subjects with low-serum $T_3$ and high $rT_3$ concentrations ("low $T_3$ syndrome") did not show any survival advantage and had lower baseline physical activity. The authors suggested that higher serum $rT_3$ concentrations may result from a decreased peripheral metabolism of thyroid hormones due to the ageing process itself and/or disease and may reflect a catabolic state although, a certain degree of lower activity of the thyroid hormone axis might be beneficial during the aging process.

All together, these findings might support the idea that mild physiologically decline of thyroid activity at the tissue level might have favorable effects in the oldest-old subjects. However, the interpretation of the predictive value of thyroid failure in old subjects has to be considered with caution, carefully defining the context and the criteria of analyzed populations. In this setting, the comparison of observational trials is not so easy and the different population analyzed should be taken into account. Indeed, there is not a unique definition of TSH limits for patient classification in the clinical studies or statistical analysis, and the population of published trials is very heterogeneous differing for the age of enrolled patients, life styles, comorbidities, treatments, ethnics etc. Although in some selected elderly subjects (specific ethnic population or very old subjects) (subtle) thyroid failure might be a beneficial factor or a longevity associated character, one of the most debated issues regarding the health consequences of (subclinical) hypothyroidism in the elderly is represented by the potential increase of ischemic heart disease (IHD) or other CVDs as well as cognitive impairment (Mariotti et al., 2005).

## 5. Subclinical hypothyroidism and cardiovascular diseases

### 5.1. Pathophysiology

The most characteristic and common symptoms and signs, experienced by patients with thyroid disease, are those related to the cardiovascular (CV) system (Klein & Ojamaa, 2001). Both hyperthyroidism and hypothyroidism produce changes in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistances (SVR) (Dillmann, 2002). Indeed, either hyper or hypothyroidism can produce heart arrhythmias, although it is less well recognized that hypothyroidism may predispose to specific dysrhythmias (Klein & Danzi., 2007). Cardiovascular signs and symptoms of hypothyroidism include bradycardia, mild (diastolic) hypertension, narrowed pulse pressure, cold intolerance, and fatigue (Klein & Ojamaa, 2001).

Subclinical hypothyroidism might be interpreted as an intermediate alteration between overt dysfunction and euthyroidism, consequently, the modifications of CV system observed in sHT qualitatively resemble those produced by overt hypothyroidism even if less evident. Accordingly, several evidences indicated that there is a direct association between serum TSH value and CV alterations as well as blood pressure, cholesterol level etc. (Biondi & Cooper, 2008; Asvold et al., 2007). There are many evidences that, in major part of the cases of thyroid patients, cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated (Kahaly et al., 2005). Moreover, there is substantial evidence that overt hypothyroidism and also sHT, although to a lesser extent, may alter several of the traditional risk factors for ischemic CVD.

The effects of thyroid hormone deficiency on the cardiovascular system have been evaluated from many points of view as heart diastolic and systolic dysfunction, endothelial dysfunction, hypertension, metabolic alterations and impaired exercise performance (Biondi & Cooper, 2008). To understand well the impact of sHT on CV system and the consequent

increased risk of cardiovascular events, it is necessary to review the molecular effects of $T_3$ and $T_4$, and the modifications that they exert in myocytes, endothelium, vascular muscle cells, intermediate metabolism etc. The decrease of cardiac output associated with hypothyroidism results, in part, from changes in cardiac gene expression, specifically reduced expression of the sarcoplasmic reticulum Ca2-ATPase, and increased expression of its inhibitor, phospholamban (Belke et al., 2007). In addition, these molecular changes explain the prolonged isovolumic relaxation phase of the hypothyroid myocardium and early reversible diastolic impairment (Klein & Danzi, 2007). Interestingly, this mechanism functionally resembles the progressive age related myocardium modification, in which increased fibrosis, myocyte hypertrophy and myocyte loss result in increased myocardial stiffness leading to diastolic heart failure (Biondi & Cooper, 2008).

Triiodothyronine produces a decrease in systemic vascular resistance enhancing arteriole dilatation of the peripheral circulation (Klein & Ojamaa, 2001). The endothelium and smooth muscle cells are biological targets of action of $T_3$ with a vasodilatation effect, also in coronary arteries (Ojamaa et al., 1996). As stated by Klein & Ojamaa (2001), $T_3$ induces in vitro relaxation of smooth muscle cells with a non-genomic effect and independently of nitric oxide production (Klein & Ojamaa, 2001). Indeed, Ojamaa et al. (1996) found that the exposure of primary cultures vascular smooth muscle cells to $T_3$ resulted in cellular relaxation within 10 min while, the exposure of primary cultures of vascular endothelial cells to the same hormone did not induce nitric oxide production, suggesting a direct effect of $T_3$ on vascular smooth muscle cells. By contrast, Colantuoni et al. (2005) showed that *in vivo* thyroid hormone induced vasodilatation is delayed and mainly dependent to nitric oxide. The aim of their study was to assess the effects of topically applied $T_3$ and $T_4$ on the arterioles of hamster cheek pouch microcirculation *in vivo* by visualizing microvessels through a fluorescent microscopy technique. Topical application of both $T_3$ and $T_4$ consistently induced a dose-dependent dilation of arterioles within few minutes. However, $T_3$-induced dilation was countered by the inhibition of nitric oxide synthase with specific *i*Nos inhibitors. These discrepancies between *in vitro* and *in vivo* findings might be related to differences in experimental procedures and to the fact that *in vivo* conditions are more complex than *in vitro* insolated cell cultures (Galli et al., 2010). The vascular action of $T_3$ and $T_4$ has been also reported to be associated with the modulation of gene expression related to endothelial homeostasis like angiotensin receptors (Fukuyama et al., 2003), reinforcing the hypothesis that thyroid hormones mainly target the vasculature. Accordingly, a cross-sectional study on 30728 patients without previous known thyroid diseases revealed a linear positive association between TSH level and systolic and diastolic blood pressure (Asvold et al., 2007). In this setting, Fommei et al. (2002) reported the physiological relationships between blood pressure and neuro-humoral modifications induced by acute hypothyroidism [levothyroxine ($LT_4$) withdrawal] in normotensive subjects. During the hypothyroid state daytime arterial blood pressure (mainly diastolic) significantly increased along with noradrenaline and adrenaline levels. By contrast, plasma renin activity remained unchanged. These data, besides confirming the role of thyroid hormones in systemic arterial blood pressure homeostasis, suggest that sympathetic and adrenal reversible activation may contribute to the development of arterial hypertension in human hypothyroidism (Fommei et al., 2002).

Arterial hypertension related to thyroid hormone deficiency may result in aortic stiffness and early atherosclerosis. In this setting, aortic stiffness was studied in 30 patients who never received treatment for hypertension or hypothyroidism, 15 patients with normal blood pressure and hypothyroidism, and 15 patients with hypertension and normal thyroid function. Aortic diameter, evaluated by M-mode echocardiography and blood pressure measured by sphygmomanometer, were assessed to calculate the aortic stiffness index. Patients with hypertension and hypothyroidism have increased aortic stiffness, which was decreased in all patients by hormone replacement therapy, although hypertension resulted completely reversible in 50% of the patients (Dernellis et al., 2002). In addition, it has been hypothesized that thyroid hormone deficiency might be related to endothelial dysfunction. In this area, Lekakis et al. (1997) enrolled 35 subjects with various serum TSH levels to assess endothelial and smooth muscle responses of the brachial artery by high-resolution ultrasound imaging. Results of this study showed that flow-mediated, endothelium-dependent (FMD) vasodilatation progressively impaired with increasing serum TSH value; the phenomenon appearing still in patients with TSH value within the normal reference range (2.01-4.00 microIU/mL) (Lekakis et al., 1997). Furthermore, in order to assess vascular reactivity and NO availability in patients with sHT and its relation to the serum lipid profile, Taddei et al. (2003) evaluated, by strain-gauge plethysmography, the forearm blood flow response to intrabrachial acetylcoline, an endothelium-dependent vasodilator, at baseline and during infusion of the *e*NO synthase inhibitor Ng-monomethyl-L-arginine (L-NMMA). Results from sHT patients were compared with two groups of euthyroid control subjects, one with normal lipid profile and one with mildly elevated serum TC levels, comparable to those of sHT patients. They found that vasodilation in response to acetylcholine of patients affected by sHT was reduced as compared to that of both groups of euthyroid control subjects. Similarly, L-NMMA blunted the vasodilation in response to acetylcholine either in normolipemic or in mildly hypercholesterolemic controls, whereas it was ineffective in sHT patients, thus suggesting a reduced NO availability due to impaired NO synthase induced by sHT *per se*. Interestingly, six months of euthyroidism induced by $LT_4$ replacement increased acetylcholine vasodilation and restored L-NMMA inhibition. Subsequently, the same group (Taddei et al. 2006) demonstrated that endothelial dysfunction of a cohort of sHT patients with autoimmune thyroiditis was, at least partially, related to oxidative stress and low-grade systemic inflammation. Indeed, sHT patients had higher plasma C-reactive protein (CRP) levels as compared to euthyroid controls, and endothelium dysfunction was significantly improved after either local infusion of vitamin C or systemic administration of indomethacin, a non-selective cyclo-oxygenase (COX) inhibitor. Comparable results were obtained after administration of celecoxib, a selective COX-2 inhibitor, thus suggesting that an association between thyroid function and low-grade systemic inflammation could be postulated. Accordingly, several studies (Kvetny et al., 2004; Luboshitzky et al., 2004; Christ-crain et al., 2003; Lee et al., 2004) investigated the possible relationship between TH deficiency and serum CRP level, that was mostly found higher in hypothyroid patients, although unaffected by $LT_4$ therapy (Christ-crain, 2003).

Another concurring factor for developing early atherosclerosis in hypothyroidism is represented by the metabolic alterations induced by hormone deficiency. Hypothyroidism is

characterized by hypercholesterolaemia with elevation of low-density lipoprotein cholesterol (LDLc) levels because of decreased fractional clearance of LDLc by a reduced number of the receptors in the liver (Duntas et al., 2002; Staub et al., 1992). Early studies in hypothyroid humans, using isotopically labeled LDLc, demonstrated a prolonged half-life of LDLc due to a decreased catabolism; this effect was reversible with $LT_4$ therapy (Walton et al., 1965). Accordingly, the addition of $T_3$ to human fibroblast cultures induced a higher LDLc degradation, through an increase in LDLc receptor number, without any receptor affinity change (Chait et al., 1979). Molecular mapping has revealed functional thyroid response elements in the promoter region of the LDLc receptor. Indeed, specific stimulation by $T_3$ of a chimeric gene resulting from the LDLc receptor promoter linked to a reporter gene, cotransfected with the isoform of the thyroid hormone receptor into a hepatic cell line, has been reported (Bakker et al., 2001). Moreover, the deletion of the upstream thyroid response elements in the LDLc receptor promoter inhibited $T_3$-mediated reporter gene activity (Cappola et al., 2003). Although the relationship between thyroid function and altered lipid profile is well documented in overt hypothyroidism it is still controversial in sHT (Biondi & Cooper, 2012). The conflicting results about lipid profile and sHT might reflect differences in study design as well as in age, gender, and ethnicity of the study cohorts (Palmieri et al., 2002).

Various changes in the coagulation-fibrinolytic system have been described in patients with thyroid dysfunction although, data regarding the association between thyroid failure and modifications of the coagulation-fibrinolytic system are still controversial (Chadarevian et al., 2001; Canturk et al., 2003; Muller et al., 2001). The influence of thyroid hormone on the coagulation fibrinolytic system is mainly mediated by the interaction between the hormone and its receptors (Shih et al., 2004). Various abnormalities have been described, ranging from subclinical laboratory abnormalities to major hemorrhages or fatal thromboembolic events (Squizzato et al. 2007). The relationship between thyroid hormones and the coagulation system is, however, often ignored. One of the reasons could be that, although several in vivo abnormalities have been reported in patients with hypothyroidism and hyperthyroidism, most published studies focus on laboratory measurements, and good studies on the relationship between thyroid dysfunction and clinically manifest bleeding or thrombosis are lacking. However, most studies confirm that both overt hyper- and hypothyroidism modify the coagulation-fibrinolytic balance. Thyroid hormone excess or deficit is the probable main pathophysiological mechanism and, patients with overt hypo- and hyperthyroidism appear to have an increased risk of bleeding and of thrombosis, respectively (Squizzato et al. 2007).

Overall, these findings support a biologically plausible role for hypothyroidism in increasing the risk of atherosclerotic CV disease, via the increase in circulating levels of LDLc, systemic (diastolic) hypertension, diastolic dysfunction and heart failure as well as an imbalance of the coagulation system and direct effects on vascular smooth muscle (Cappola et al., 2003). However, the actual relationship between sHT and increased cardiovascular risk is still unresolved and represents one of the most common topics in endocrinology, leading to several controversies concerning the clinical management of sHT patients (Turemen et al., 2011).

## 5.2. Clinical evidences

As above described, thyroid hormone deficiency is associated to several cardiovascular and metabolic abnormalities (Biondi & Cooper, 2008; Caraccio et al., 2003; Dardano & Monzani, 2008). Indeed, thyroid failure may favour the onset of several CV risks like diastolic hypertension, hyperlipidemia, vascular stiffness, heart failure etc. However, although the relationship between overt hypothyroidism and coronary heart disease (CHD) as well as increased CHD mortality is widely recognized (Klein, 2004), the clinical significance of sHT is still controversial and conflicting opinions remain on the association between sHT and CVD or mortality, especially in older people (Biondi & Cooper, 2008; Monzani et al., 2006). Indeed, data regarding the association between sHT and CHD or total mortality are contradictory among various population based, observational studies (Aho et al., 1984; Cappola et al., 2004; Hak et al., 2000; Walsh et al., 2005).

One of the first large study (Whickham Survey) that evaluated vascular events over 20 years in community-dwelling subjects stratified by thyroid function and thyroid autoantibody status did not show any association between CHD and sHT (Vanderpump et al., 1995). This result appeared at odds with the findings of other subsequent cohort studies (Hak et al., 2000; Imaizumi et al., 2004; Walsh et al., 2005). However, while reanalyzing incident CHD events and mortality in Whickham participants including $LT_4$ replacement during follow-up as covariate, a significant increment of incident CHD events and mortality was found in individuals with baseline sHT (Razvi et al., 2010). Based on the results of this analysis, it would appear that treatment of sHT might be associated with reduced mortality as well as CHD events. However, besides the small total number of events in each group of sHT participants, there is a potential for bias in this retrospective observational analysis (i.e. sHT patients who were treated may have been more health conscious leading to a healthy user bias). Therefore, these results need to be interpreted with caution until a large prospective, randomized controlled trial will be available. The inconsistency in results among several studies (Aho et al., 1984; Hak et al., 2000; Cappola et al., 2004; Razvi et al., 2010; Walsh et al., 2005) may be due to differences in the enrolled populations as well as the duration either of tissues exposure to sHT or of follow-up of the various studies. Nonetheless, meta-analyses of CHD events and sHT have shown that such an association probably exists (Razvi et al., 2008; Rodondi et al., 2006), especially in younger cohorts. In this regard, to assess the risks of CHD and total mortality for adults with sHT, Rodondi et al. (2010) carried out a large meta-analysis on 11 prospective cohorts, enrolling a total of 55,287 participants. The risk of CHD events was examined in 25,977 participants from 7 cohorts with available data. Among 55,287 adults, 3450 had sHT (6.2%) and 51,837 were euthyroid. The Authors found that the risk of CHD events and mortality increased with higher TSH concentrations. Results were similar after adjustment for traditional cardiovascular risk factors. Moreover, this pooled analysis showed a higher rate of CHD events in sHT patients with higher TSH levels (>10 mIU/L). These data are consistent with most previous meta-analysis and several naturalistic studies, showing an increased risk of CHD events associated with sHT (Hak et al., 2000; Singh et al., 2007; Walsh et al., 2005).

These studies, however, did not accurately explore potential differences related to participant characteristics like age, even if older people represented large a share of the population. In this setting, the pooled analysis of large cohort of patients may be affected by hypothetical bias and may not investigate specific classes of patients like very old people versus moderate elderly patients or other specific conditions affecting the clinical outcome. Ochs et al. (2008) analysed in a meta-analysis the effect of ageing on sHT associated CV events and total mortality. Similar to previous meta-analysis, they found a pattern of modestly increased risk for CHD and mortality associated with sHT. A weak evidence for statistical heterogeneity among individual study findings was found, and age explained part of the heterogeneity for the association between sHT and CHD, with an increased risk for CHD only in cohorts with a younger mean age. Accordingly, Cappola et al. (2006), in a large population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older, concluded that the results did not support the hypothesis of an association between unrecognized sHT and increased CV events or mortality. On the other hand, one cross-sectional study with subgroup analyses by age found that increased risk for CHD was present in younger sHT participants only (<50 years old) (Kvetny et al. 2004). In this regard, a prospective, observational, population-based follow-up study carried out on 599 participants followed up from age 85 years through age 89 years showed no association between serum TSH and $FT_4$ levels and disability in daily life, depressive symptoms, and cognitive impairment at baseline or during follow-up. Moreover, increasing serum TSH levels were associated with a lower mortality rate that remained after adjustments for baseline disability and health status (Gusseklo et al. 2004). Overall, these data support the hypothesis that in the oldest old population, individuals with abnormally high levels of TSH do not experience adverse effects and may have a prolonged life span. The study focused on a specific class of patients (very older people), for this reason, the results should be rigorously interpreted, also considering the weakness of observational studies. However, these data together with the results obtained by Rozing et al., (2010) that demonstrated a possible genetic predisposition of nonagenarians to a decrease function of hypothalamus-pituitary-thyroid axis, suggest that the oldest old may represent a different population respect to moderate old people or young adults. Potential explanations for these age differences might be competing mortality among older adults (for example, due to cancer) or more competing risk factors for CHD among older adults (for example, age or sex). However, the above reported substantial age differences should be interpreted with caution, given the possibility of ecological fallacy without individual patient data and, should be confirmed by stratified analyses in future prospective cohort studies with a wide age range (Egger et al., 2001).

There are few clinical studies evaluating the effects of hormone replacement in sHT subjects and none aimed to determine the impact of therapy on total mortality especially in older people. Previous research in this area has shown contradictory results, with some randomized, controlled trials (number of patients ranging from 45 to 63) showing an improvement in the atherogenic lipid profile as well as surrogate endpoints of atherosclerosis (Meier et al., 2001; Caraccio et al., 2002; Monzani et al., 2004) but others (number of patients ranging from 17 to 35) showing no difference (Cooper et al., 1984; Jaeschke et al., 1996; Kong et al., 2002; Nystrom et al., 1988). Recently, Razvi et al. (2007)

conducted a randomized, double-blind, crossover study to determine the short-term (12 weeks) effect of $LT_4$ replacement therapy in 100 sHT patients (age range 18-80 yrs, mean 53.8) with serum TSH level>4.0 mIU/L. Primary end points included: serum cholesterol level variations along with improvement in flow-mediated dilation (FMD) as a marker of vascular endothelial function. $LT_4$ treatment significantly reduced either TC or LDLc concentrations, and improved FMD, as compared to placebo group. Moreover, multivariate analysis showed that increased serum $FT_4$ level was the most significant variable predicting reduction in TC or FMD improvement. The Authors hypothesized that if the reduction of LDLc level would be long term sustained, this would result in a relative reduction in 10-yr CV mortality of about 10%, thus supporting the use of $LT_4$ replacement therapy also in patients with slightly elevated TSH value. Long-term studies are nonetheless required to confirm whether these apparent short-term benefits will translate into reduction in CV mortality and morbidity. Moreover, notwithstanding the wide age range of the studied patients, these results cannot directly transfer to the elderly, especially the oldest old population.

In summary, conflicting results among large prospective cohort studies regarding the relationship between sHT and cardiovascular disease might reflect differences in participants such as age, gender, TSH value, or pre-existing cardiovascular disease. However, as demonstrated by some meta-analyses, the negative effect of sHT on cardiovascular risk is well established in younger people while in moderately old population (>65 and <85 years) it appears no longer evident. Moreover, in the oldest old people (>85 years) one study suggested that high levels of TSH not only do not exert adverse effects but also may favor a prolonged life span (Fig. 1). In this regard, elderly population can be interpreted as a heterogeneous group, nonagenarians representing a genetically selected cluster. Indeed, these subjects may have a genetic background that protects from CVD and/or thyroid hormone deficiency, thus suggesting an intriguing link between gene, thyroid status and longevity.

## 6. Thyroid function and cognitive impairment

Thyroid hormones are crucial for brain development and function: thyroid failure at any age causes cognition to deteriorate because thyroid hormones are essential for adequately sustaining the energy (glucose)-consuming processes needed for neurotransmission, memory, and other higher brain functions (Herholz, 2010; Patel et al., 2011). Low brain uptake of glucose is commonly associated with deteriorating cognition and Alzheimer's disease and can be present decades before clinical evidence of Alzheimer's disease occurs (Herholz, 2010). Brain hypometabolism therefore appears to be a precursor lesion increasing the risk of at least some forms of cognitive decline. Elevated TSH levels in the range found in patients with overt hypothyroidism have been described to be associated with impaired function in many cognitive domains, but the association between sHT and cognition is less clear (Graham et al., 1997; Gardner, 2004; Chavanne et al., 2011). On the other hand, several cross-sectional studies have observed that high or low TSH levels, still within the normal range (clinically euthyroid), are each related to poor cognitive performance, although some other investigations failed to demonstrate these findings (Prinz et al., 1999; Volpato et al.,

2002). It should be underlined, however, that different cognitive deficits possibly related to thyroid failure do not necessarily follow a consistent pattern, and $LT_4$ treatment may not always completely restore normal functioning in patients with hypothyroidism. Giving these premises, we summarize here the growing, conflicting literature on the relationship between cognitive performance and thyroid function from an ageing perspective.

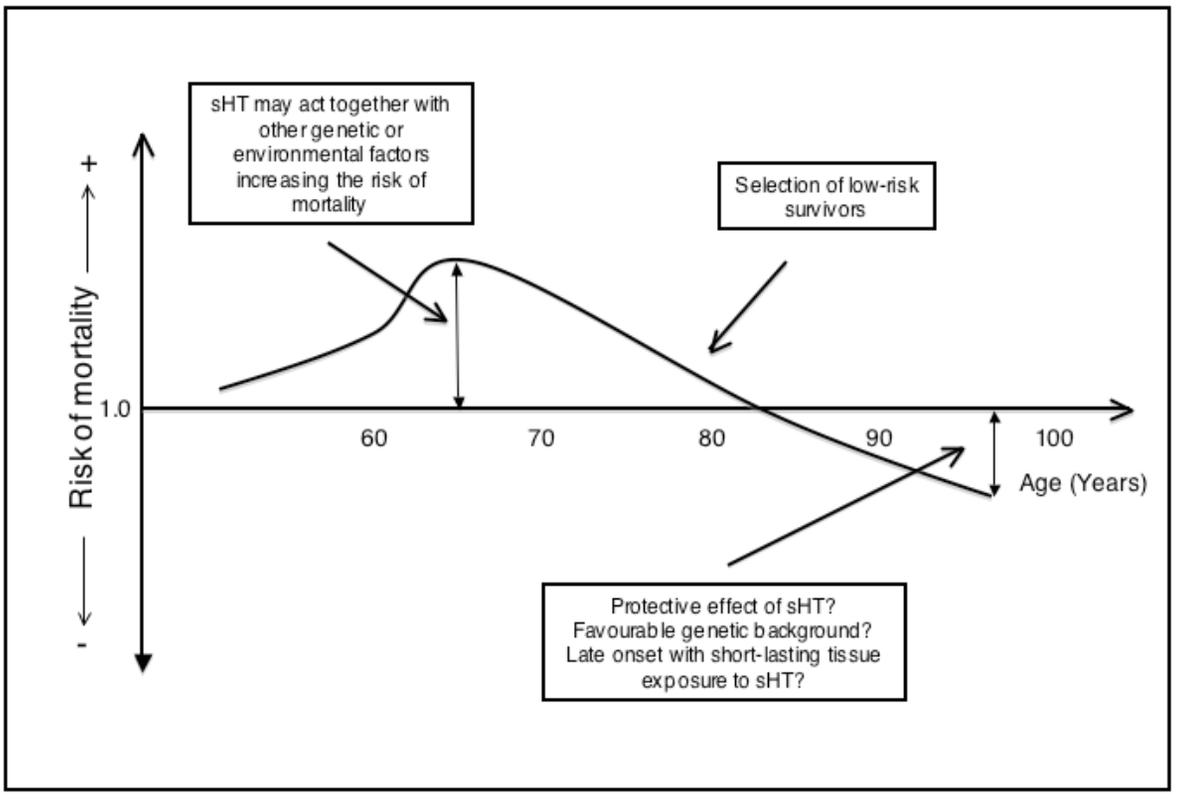


**Figure 1.** Hypothetical relationship between risk of total mortality and age in patients with subclinical hypothyroidism (sHT) (Modified from Mariotti, 2005).

Subclinical hypothyroidism and cognitive function have been investigated in several preclinical experiments and clinical trials. To date, the actual relationship between mild thyroid hormone deficiency and cognitive impairment in the elderly is not well understood. In fact, there are several contrasting data resulting from cross-sectional and clinical experiments (Gussekloo et al., 2004; Roberts et al., 2006; Tan et al., 2008; Ceresini et al., 2009). Moreover, the available published data, in many cases, are not easily comparable considering the differences in inclusion criteria of each clinical study. Several small observational and interventional studies have reported an association, although not homogeneously, between cognitive impairment and sHT and, in some cases, it was described a cognitive performance improvement after $LT_4$ replacement (Etgen et al., 2011; Monzani et al., 1993; Osterweil et al., 1992; St. John et al., 2009; Volpato et al., 2002). Moreover, Hogervost et al. (2008) studied the association between TSH and $FT_4$ levels and cognition at baseline and after 2 years of follow-up in 1047 participants over 64 years of age, without physical frailty or severe cognitive impairment. The study showed that elevated TSH levels were associated with lower MMSE performance at baseline, independently of

$FT_4$ value, age, sex, education and mood. Interestingly, epidemiological surveys using the revised Wechsler Adult Intelligence Scale (WAIS-R) and the Mini-Mental State Examination (MMSE) showed a relationship between plasma thyroid hormone levels and cognitive status in subjects with thyroid function still within the upper limit of the normal range (Prinz et al., 1999; Volpato et al., 2002). Accordingly, altered plasma thyroid hormone concentrations have been recognized as a risk factor for cognitive impairment or dementia (Bulens, 1981; Kalmijn et al., 2000; Tan et al., 2008). More specifically, with the increasing sensitivity of neuropsychological tools, it has become evident that thyroid hormone deficiency might produce measurable deficits in very specific neuropsychological functions (Zoeller & Rovet 2004). In this regard, in a recent prospective, open-labeled interventional study, cognitive impairment associated with (mild) thyroid failure appeared predominantly mnemonic in nature, suggesting that the etiology is not indicative of general cognitive slowing (Correia et al., 2009).

Conflicting data were obtained by large, population-based studies, leading to uncertain conclusions regarding the association between (mild) thyroid failure and cognition (Gussekloo et al., 2004; Roberts et al., 2006; Tan et al., 2008; Ceresini et al., 2009). In this setting, one critical point that could affect the results of these studies is the diverse age groups of the enrolled patients (moderate or very old) as well as the presence of comorbidity. Cognitive impairment observed in older sHT individuals might be also an epiphenomenon of the increased risk for atherosclerosis or the effect of thyroid hormone on vasculature. Indeed, arterial stiffness is a potential mechanism of advancing cognitive decline in sHT (Yamamoto et al., 2012) and elevated TSH values might negatively affect vascular function through systemic low-grade inflammation (Taddei et al., 2006). Moreover, whereas in moderate older people sHT might produce a detrimental effect on cognitive performance, in very old individuals (mild) thyroid failure might be not associated to a negative outcome (Gussekloo et al., 2004; Tan et al., 2008). To determine whether subclinical thyroid dysfunction should be treated in old age and the long-term impact of thyroid dysfunction on performance and survival in the elderly, a prospective, observational, population-based survey was carried out within the Leiden 85-Plus Study. A total of 599 participants were followed up from age 85 years through age 89 years. Plasma levels of TSH and $FT_4$ were not associated with disability in daily life, depressive symptoms, and cognitive impairment at baseline or during follow-up. Conversely, increasing levels of TSH were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status (Gussekloo et al., 2004). It is noteworthy, however, that similarly to CHD risk, these results should be confirmed by stratified analyses in future prospective large cohort studies with a wide age range.

Another important aspect is the possible relationship between sHT and the risk to develop Alzheimer disease (AD). On this basis, many studies investigated a possible association between AD and thyroid dysfunction. Increasing evidence supports an extensive interrelationship between thyroid hormones and the cholinergic system, which is selectively and early affected in AD. Thyroid hormones negatively regulate expression of the amyloid-beta protein precursor, which plays a key role in the development of AD (Belakavadi et al.,

2011). In a study aimed to examine the feasibility of using thyroid hormone as a therapeutic agent for AD, mice were injected intra-hippocampally with aggregated amyloid beta-peptide (Abeta) to produce AD animal model. Intraperitoneal administration of $LT_4$ into Abeta-induced AD model mice prevented their cognitive impairment and improved their memory function. The authors suggested that the mechanisms of $LT_4$ treating AD might be associated with regulating cholinergic function, protecting the brains of AD model mice against damage and rescuing hippocampal neurons from apoptosis. The results of this study seem indicate that the use of thyroid hormone may have some therapeutic potential in AD (Fu et al., 2010). Accordingly, in a post mortem study it was evaluated the brain thyroid hormone levels in AD measured with radioimmunoassay (RIA) samples of prefrontal cortex of patients with pathologically confirmed AD and controls without any primary neurological disease. Thyroxine levels did not differ between groups while $T_3$ levels were significantly lower in Alzheimer's brains respect to controls. These results suggest that the conversion of $T_4$ to $T_3$ may be altered in advanced AD, perhaps due to modifications in deiodinase activity, and the reduced hormone conversion might be associated with both AD pathology and the clinical presentation of dementia (Davis et al., 2008). Moreover, Tan et al. (2008) related serum TSH concentrations to the risk of Alzheimer disease in 1864 cognitively intact, euthyroid participants of the Framingham original cohort (mean age 71 years). During a mean follow-up of 12.7 years, 209 participants (142 women) developed AD. Women in the lowest (<1.0 mIU/L) and highest (>2.1 mIU/L) tertiles of serum TSH concentration were at increased risk for AD compared with those in the middle tertile while, TSH levels were not related to AD risk in men. On the other hand, at odds with these findings, the InChianti study showed an association between subclinical hyperthyroidism and cognitive impairment without any correlation with mild thyroid failure in a large cohort of older people (Ceresini et al., 2009).

In conclusion, a certain degree of cognitive (mnemonic) impairment is generally recognized in case of overt hypothyroidism while, the relationship between cognition and sHT is still a disputed field, and it remains unclear whether to treat or not this kind of patients. In particular, there is little or no consensus in the literature whether thyroid failure is associated with impaired cognitive performance in the elderly, especially in the oldest old population. While interpreting the above reported conflicting results it should be outlined, however, that thyroid hormone concentrations change with age and cognitive decline is often concomitant with ageing; therefore, a reciprocal relationship could exist between changes of thyroid function and cognitive decline during normal ageing.

## 7. Conclusions

Levothyroxine replacement therapy for reducing sHT associated CV risk factors is still controversial, especially in the elderly. The lack of specific randomized trials, enrolling either old or very old subjects, aimed to evaluate the efficacy of hormonal replacement on overall survival and cardiovascular risk reduction as well as the possible negative effects of $LT_4$ supplementation, makes the decision to treat elderly people very difficult. Generally,

$LT_4$ replacement therapy should be considered for three main reasons: i) to prevent progression of sHT to overt hypothyroidism which, however, is much more important in young patients; ii) to reduce the symptoms associated with mild thyroid failure, which are especially scarce in the elderly; iii) to improve the lipid profile and other risk factors that may contribute to atherosclerosis progression and CV events.

Subclinical thyroid failure causes changes in cardiac function similar to, but less marked than, those occurring in patients with overt hypothyroidism. Diastolic dysfunction both at rest and upon effort is the most consistent cardiac abnormality in patients with sHT, even in those with slightly elevated TSH levels (>6 mIU/L) (Arem et al., 1996; Biondi & Cooper, 2012;). Mild thyroid failure may also increase diastolic blood pressure as a result of increased systemic vascular resistances (Faber et al., 2002; Kahaly, 2000; Luboshitzky et al., 2002). Interestingly, restoration of euthyroidism by $LT_4$ replacement is able to reduce systemic hypertension as well as improve left ventricular myocardial function (Brenta et al., 2003). Moreover, sHT has been claimed to be a risk factor for atherosclerosis and ischemic CVD, therefore, it is appropriate to consider whether treatment confers some protection from such a risk. Although a consensus is still lacking, the strongest evidence for a beneficial effect of levothyroxine replacement therapy is the substantial demonstration that restoration of euthyroidism can lower TC and LDLc levels in most patients with sHT. Besides hypercholesterolemia several emerging risk factors for CHD have been claimed to be associated with sHT. Among them, altered coagulation parameters, endothelial dysfunction, and elevated CRP levels are consistently regarded to combine with the raised LDLc levels of untreated patients with sHT to enhance the cardiovascular risk.

As a whole, these findings suggest that the decision to treat patients with sHT should depend on the presence of risk factors, rather than on a TSH threshold. International organizations and guidelines suggest starting replacement therapy in patients who have TSH concentrations greater than 10 mIU/liter and in those with evidence of autoimmunity, and in symptomatic patients with TSH levels between 4.5 and 10 mIU/L (Gharib et al., 2005a,b; Surks et al., 2004). However, the treatment of sHT patients, especially the elderly, must be individualized once any underlying coexisting morbidity or pharmacologic interference has been excluded. Generally $LT_4$ replacement results effective and safe in young patients, providing that excessive dosing is avoided by monitoring serum TSH level. Indeed, $LT_4$ replacement therapy can always be discontinued if there is no apparent benefit. It is noteworthy that, once a stable, elevated TSH value is detected, the costs of annual follow-up with clinical assessment and laboratory testing are relatively similar whether or not a patient is treated with $LT_4$ (Cooper et al., 2001). On the other hand, the possibility that restoring euthyroidism may be harmful in the older population has been raised, and should be taken into account in making the decision of treating such patients, especially those older than 85 years. In this setting, hormonal replacement might be considered in old patients on the base of a specific evaluation of the possible thyroid dysfunction causes, pre-existent cardiovascular risk including cholesterol level, hearth failure as well as the presence of comorbidities or frailty and the level of TSH. However, until adequate data are accumulated, clinicians should consider each patient a unique situation, and best clinical practice continues to be a combination of clinical judgment and the patient's preference.

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## 8. References

Aho, K., Gordin, A., Palosuo, T., Punsar, S., Valkeila, E., Karvonen, M., Inkovaara, J., Pasternack, A. (1984). Thyroid autoimmunity and cardiovascular diseases. Eur Heart J, Vol. 5, No. 1 (Jan 1984), pp. 43-46, issn 0195-668X (Print) 0195-668X (Linking).

Andersen, S., Pedersen, K.M., Bruun, N.H., Laurberg, P. (2002). Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab, Vol. 87, No. 3 (Mar 2002), pp. 1068-1072, issn 0021-972X (Print) 0021-972X (Linking).

Arem, R., Rokey, R., Kiefe, C., Escalante, D.A., Rodriguez, A. (1996). Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. Thyroid, Vol. 6, No. 5 (Oct 1996), pp. 397-402, issn 1050-7256 (Print) 1050-7256 (Linking).

Ashizawa, K., Imaizumi, M., Usa, T., Tominaga, T., Sera, N., Hida, A., Ejima, E., Neriishi, K., Soda, M., Ichimaru, S., Nakashima, E., Fujiwara, S., Maeda, R., Nagataki, S., Eguchi, K., Akahoshi, M. (2010). Metabolic cardiovascular disease risk factors and their clustering in subclinical hypothyroidism. Clin Endocrinol (Oxf), Vol. 72, No. 5 (May 2010), pp. 689-695, issn 1365-2265 (Electronic) 0300-0664 (Linking).

Asvold, B.O., Bjoro, T., Nilsen, T.I., Vatten, L.J. (2007). Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. J Clin Endocrinol Metab, Vol. 92, No. 3 (Mar 2007), pp. 841-845, issn 0021-972X (Print) 0021-972X (Linking).

Atzmon, G., Barzilai, N., Hollowell, J.G., Surks, M.I., Gabriely, I. (2009). Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab, Vol. 94, No. 4 (Apr 2009), pp. 1251-1254, issn 1945-7197 (Electronic) 0021-972X (Linking).

Bakker, S.J., ter Maaten, J.C., Popp-Snijders, C., Slaets, J.P., Heine, R.J., Gans, R.O. (2001). The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab, Vol. 86, No. 3 (Mar 2001), pp. 1206-1211, issn 0021-972X (Print) 0021-972X (Linking).

Baloch, Z., Carayon, P., Conte-Devolx, B., Demers, L.M., Feldt-Rasmussen, U., Henry, J.F., LiVosli, V.A., Niccoli-Sire, P., John, R., Ruf, J., Smyth, P.P., Spencer, C.A., Stockigt, J.R. (2003). Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid, Vol. 13, No. 1 (Jan 2003), pp. 3-126, issn 1050-7256 (Print) 1050-7256 (Linking).

Basaria, S., Cooper, D.S. (2005). Amiodarone and the thyroid. Am J Med, Vol. 118, No. 7 (Jul 2005), pp. 706-714, issn 0002-9343 (Print) 0002-9343 (Linking).

Belakavadi, M., Dell, J., Grover, G.J., Fondell, J.D. (2011). Thyroid hormone suppression of beta-amyloid precursor protein gene expression in the brain involves multiple epigenetic regulatory events. Mol Cell Endocrinol, Vol. 339, No. 1-2 (Jun 6 2011), pp. 72-80, issn 1872-8057 (Electronic) 0303-7207 (Linking).

Belke, D.D., Gloss, B., Swanson, E.A., Dillmann, W.H. (2007). Adeno-associated virus-mediated expression of thyroid hormone receptor isoforms-alpha1 and -beta1 improves contractile function in pressure overload-induced cardiac hypertrophy. Endocrinology, Vol. 148, No. 6 (Jun 2007), pp. 2870-2877, issn 0013-7227 (Print) 0013-7227 (Linking).

Bemben, D.A., Winn, P., Hamm, R.M., Morgan, L., Davis, A., Barton, E. (1994). Thyroid disease in the elderly. Part 1. Prevalence of undiagnosed hypothyroidism. J Fam Pract, Vol. 38, No. 6 (Jun 1994), pp. 577-582, issn 0094-3509 (Print) 0094-3509 (Linking).

Billewicz, W.Z., Chapman, R.S., Crooks, J., Day, M.E., Gossage, J., Wayne, E., Young, J.A. (1969). Statistical methods applied to the diagnosis of hypothyroidism. Q J Med, Vol. 38, No. 150 (Apr 1969), pp. 255-266, issn 0033-5622 (Print) 0033-5622 (Linking).

Biondi, B., Cooper, D.S. (2008). The clinical significance of subclinical thyroid dysfunction. Endocr Rev, Vol. 29, No. 1 (Feb 2008), pp. 76-131, issn 0163-769X (Print) 0163-769X (Linking).

Biondi B., Cooper, D.S. (2012). Subclinical thyroid disease. Lancet, (Jan 20 2012). [Epub ahead of print] PubMed PMID: 22273398. 0140-6736 (Linking)

Brenta, G., Mutti, L.A., Schnitman, M., Fretes, O., Perrone, A., Matute, M.L. (2003). Assessment of left ventricular diastolic function by radionuclide ventriculography at rest and exercise in subclinical hypothyroidism, and its response to L-thyroxine therapy. Am J Cardiol, Vol. 91, No. 11 (Jun 1 2003), pp. 1327-1330, issn 0002-9149 (Print) 0002-9149 (Linking).

Bulens, C. (1981). Neurologic complications of hyperthyroidism: remission of spastic paraplegia, dementia, and optic neuropathy. Arch Neurol, Vol. 38, No. 10 (Oct 1981), pp. 669-670, issn 0003-9942 (Print) 0003-9942 (Linking).

Canaris, G.J., Manowitz, N.R., Mayor, G., Ridgway, E.C. (2000). The Colorado thyroid disease prevalence study. Arch Intern Med, Vol. 160, No. 4 (Feb 28 2000), pp. 526-534, issn 0003-9926 (Print) 0003-9926 (Linking).

Canaris, G.J., Steiner, J.F., Ridgway, E.C. (1997). Do traditional symptoms of hypothyroidism correlate with biochemical disease? J Gen Intern Med, Vol. 12, No. 9 (Sep 1997), pp. 544-550, issn 0884-8734 (Print) 0884-8734 (Linking).

Canturk, Z., Cetinarslan, B., Tarkun, I., Canturk, N.Z., Ozden, M. (2003). Lipid profile and lipoprotein (a) as a risk factor for cardiovascular disease in women with subclinical hypothyroidism. Endocr Res, Vol. 29, No. 3 (Aug 2003), pp. 307-316, issn 0743-5800 (Print) 0743-5800 (Linking).

Cappola, A.R., Fried, L.P., Arnold, A.M., Danese, M.D., Kuller, L.H., Burke, G.L., Tracy, R.P., Ladenson, P.W. (2006). Thyroid status, cardiovascular risk, and mortality in older adults. JAMA, Vol. 295, No. 9 (Mar 1 2006), pp. 1033-1041, issn 1538-3598 (Electronic) 0098-7484 (Linking).

Cappola, A.R., Ladenson, P.W. (2003). Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab, Vol. 88, No. 6 (Jun 2003), pp. 2438-2444, issn 0021-972X (Print) 0021-972X (Linking).

Caraccio, N., Dardano, A., Manfredonia, F., Manca, L., Pasquali, L., Iudice, A., Murri, L., Ferrannini, E., Monzani, F. (2005). Long-term follow-up of 106 multiple sclerosis patients undergoing interferon-beta 1a or 1b therapy: predictive factors of thyroid disease development and duration. J Clin Endocrinol Metab, Vol. 90, No. 7 (Jul 2005), pp. 4133-4137, issn 0021-972X (Print) 0021-972X (Linking).

Caraccio, N., Ferrannini, E., Monzani, F. (2002). Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab, Vol. 87, No. 4 (Apr 2002), pp. 1533-1538, issn 0021-972X (Print) 0021-972X (Linking).

Carle, A., Laurberg, P., Pedersen, I.B., Perrild, H., Ovesen, L., Rasmussen, L.B., Jorgensen, T., Knudsen, N. (2007). Age modifies the pituitary TSH response to thyroid failure. Thyroid, Vol. 17, No. 2 (Feb 2007), pp. 139-144, issn 1050-7256 (Print) 1050-7256 (Linking).

Ceresini, G., Lauretani, F., Maggio, M., Ceda, G.P., Morganti, S., Usberti, E., Chezzi, C., Valcavi, R., Bandinelli, S., Guralnik, J.M., Cappola, A.R., Valenti, G., Ferrucci, L. (2009). Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. J Am Geriatr Soc, Vol. 57, No. 1 (Jan 2009), pp. 89-93, issn 1532-5415 (Electronic) 0002-8614 (Linking).

Ceresini, G., Morganti, S., Maggio, M., Usberti, E., Fiorino, I., Artoni, A., Teresi, G., Belli, S., Ridolfi, V., Valenti, G., Ceda, G.P. (2010). Subclinical thyroid disease in elderly subjects. Acta Biomed, Vol. 81 Suppl 1, No. 2010), pp. 31-36, issn 0392-4203 (Print) 0392-4203 (Linking).

Chadarevian, R., Bruckert, E., Leenhardt, L., Giral, P., Ankri, A., Turpin, G. (2001). Components of the fibrinolytic system are differently altered in moderate and severe hypothyroidism. J Clin Endocrinol Metab, Vol. 86, No. 2 (Feb 2001), pp. 732-737, issn 0021-972X (Print) 0021-972X (Linking).

Chait, A., Bierman, E.L., Albers, J.J. (1979). Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. J Clin Endocrinol Metab, Vol. 48, No. 5 (May 1979), pp. 887-889, issn 0021-972X (Print) 0021-972X (Linking).

Chavanne, D., Constans, T., Petit, A., Mondon, K., Hommet, C. (2011). Hypothyroidism and cognition in the elderly. Geriatr Psychol Neuropsychiatr Vieil, Vol. 9, No. 4 (Dec 1 2011), pp. 477-489, issn 2115-8789 (Print) 2115-7863 (Linking).

Christ-Crain, M., Meier, C., Guglielmetti, M., Huber, P.R., Riesen, W., Staub, J.J., Muller, B. (2003). Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis, Vol. 166, No. 2 (Feb 2003), pp. 379-386, issn 0021-9150 (Print) 0021-9150 (Linking).

Colantuoni, A., Marchiafava, P.L., Lapi, D., Forini, F.S., Iervasi, G. (2005). Effects of tetraiodothyronine and triiodothyronine on hamster cheek pouch microcirculation. Am J Physiol Heart Circ Physiol, Vol. 288, No. 4 (Apr 2005), pp. H1931-1936, issn 0363-6135 (Print) 0363-6135 (Linking).

Cooper, D.S. (2001). Clinical practice. Subclinical hypothyroidism. N Engl J Med, Vol. 345, No. 4 (Jul 26 2001), pp. 260-265, issn 0028-4793 (Print) 0028-4793 (Linking).

Cooper, D.S., Halpern, R., Wood, L.C., Levin, A.A., Ridgway, E.C. (1984). L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. Ann Intern Med, Vol. 101, No. 1 (Jul 1984), pp. 18-24, issn 0003-4819 (Print) 0003-4819 (Linking).

Correia, N., Mullally, S., Cooke, G., Tun, T.K., Phelan, N., Feeney, J., Fitzgibbon, M., Boran, G., O'Mara, S., Gibney, J. (2009). Evidence for a specific defect in hippocampal memory

in overt and subclinical hypothyroidism. J Clin Endocrinol Metab, Vol. 94, No. 10 (Oct 2009), pp. 3789-3797, issn 1945-7197 (Electronic) 0021-972X (Linking).

Corsonello, A., Montesanto, A., Berardelli, M., De Rango, F., Dato, S., Mari, V., Mazzei, B., Lattanzio, F., Passarino, G. (2010). A cross-section analysis of FT3 age-related changes in a group of old and oldest-old subjects, including centenarians' relatives, shows that a down-regulated thyroid function has a familial component and is related to longevity. Age Ageing, Vol. 39, No. 6 (Nov 2010), pp. 723-727, issn 1468-2834 (Electronic) 0002-0729 (Linking).

Dardano, A.M., Monzani F. (2008). Hypothyroidism and endothelial function: a markers of early atherosclerosis? . Recent Patents on Endocrine, Metabolic & Immune Drug Discovery, Vol. 2, No. 2 (May 2008 2008), pp. 79-96, issn 1872-2148.

Davis, J.D., Podolanczuk, A., Donahue, J.E., Stopa, E., Hennessey, J.V., Luo, L.G., Lim, Y.P., Stern, R.A. (2008). Thyroid hormone levels in the prefrontal cortex of post-mortem brains of Alzheimer's disease patients. Curr Aging Sci, Vol. 1, No. 3 (Dec 2008), pp. 175-181, issn 1874-6128 (Electronic).

Dayan, C.M. (2001). Interpretation of thyroid function tests. Lancet, Vol. 357, No. 9256 (Feb 24 2001), pp. 619-624, issn 0140-6736 (Print) 0140-6736 (Linking).

Dernellis, J., Panaretou, M. (2002). Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J, Vol. 143, No. 4 (Apr 2002), pp. 718-724, issn 1097-6744 (Electronic) 0002-8703 (Linking).

Diez, J.J., Iglesias, P. (2004). Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab, Vol. 89, No. 10 (Oct 2004), pp. 4890-4897, issn 0021-972X (Print) 0021-972X (Linking).

Dillmann, W.H. (2002). Cellular action of thyroid hormone on the heart. Thyroid, Vol. 12, No. 6 (Jun 2002), pp. 447-452, issn 1050-7256 (Print) 1050-7256 (Linking).

Duntas, L.H., Mantzou, E., Koutras, D.A. (2002). Circulating levels of oxidized low-density lipoprotein in overt and mild hypothyroidism. Thyroid, Vol. 12, No. 11 (Nov 2002), pp. 1003-1007, issn 1050-7256 (Print) 1050-7256 (Linking).

Egger, M., Smith, G.D., Sterne, J.A. (2001). Uses and abuses of meta-analysis. Clin Med, Vol. 1, No. 6 (Nov-Dec 2001), pp. 478-484, issn 1470-2118 (Print) 1470-2118 (Linking).

Etgen, T., Sander, D., Bickel, H., Forstl, H. (2011). Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int, Vol. 108, No. 44 (Nov 2011), pp. 743-750, issn 1866-0452 (Electronic) 1866-0452 (Linking).

Faber, J., Petersen, L., Wiinberg, N., Schifter, S., Mehlsen, J. (2002). Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. Thyroid, Vol. 12, No. 4 (Apr 2002), pp. 319-324, issn 1050-7256 (Print) 1050-7256 (Linking).

Fatourechi, V. (2009). Subclinical hypothyroidism: an update for primary care physicians. Mayo Clin Proc, Vol. 84, No. 1 2009), pp. 65-71, issn 1942-5546 (Electronic) 0025-6196 (Linking).

Fommei, E., Iervasi, G. (2002). The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab, Vol. 87, No. 5 (May 2002), pp. 1996-2000, issn 0021-972X (Print) 0021-972X (Linking).

Fu, A.L., Zhou, C.Y., Chen, X. (2010). Thyroid hormone prevents cognitive deficit in a mouse model of Alzheimer's disease. Neuropharmacology, Vol. 58, No. 4-5 (Mar-Apr 2010), pp. 722-729, issn 1873-7064 (Electronic) 0028-3908 (Linking).

Fukuyama, K., Ichiki, T., Takeda, K., Tokunou, T., Iino, N., Masuda, S., Ishibashi, M., Egashira, K., Shimokawa, H., Hirano, K., Kanaide, H., Takeshita, A. (2003). Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertension, Vol. 41, No. 3 (Mar 2003), pp. 598-603, issn 1524-4563 (Electronic) 0194-911X (Linking).

Galli, E., Pingitore, A., Iervasi, G. (2010). The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. Heart Fail Rev, Vol. 15, No. 2 (Mar 2010), pp. 155-169, issn 1573-7322 (Electronic) 1382-4147 (Linking).

Gardner, D.F. (2004). The neuromuscular system and brain in hypothyroidism, In: The Thyroid, A Fundamental and Clinical Text, Bravermann, L.E., Utiger, R.D. pp. 837841, Ninth Edition, Lippincott Williams and Wilkins, ISBN 0-7817-5047-4(HC), Philadelphia, USA

Geul, K.W., van Sluisveld, I.L., Grobbee, D.E., Docter, R., de Bruyn, A.M., Hooykaas, H., van der Merwe, J.P., van Hemert, A.M., Krenning, E.P., Hennemann, G., et al. (1993). The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. Clin Endocrinol (Oxf), Vol. 39, No. 3 (Sep 1993), pp. 275-280, issn 0300-0664 (Print) 0300-0664 (Linking).

Gharib, H., Tuttle, R.M., Baskin, H.J., Fish, L.H., Singer, P.A., McDermott, M.T. (2005a). Consensus Statement #1: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. Thyroid, Vol. 15, No. 1 (Jan 2005a), pp. 24-28; response 32-23, issn 1050-7256 (Print) 1050-7256 (Linking).

Gharib, H., Tuttle, R.M., Baskin, H.J., Fish, L.H., Singer, P.A., McDermott, M.T. (2005b). Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab, Vol. 90, No. 1 (Jan 2005b), pp. 581-585; discussion 586-587, issn 0021-972X (Print) 0021-972X (Linking).

Graham, J.E., Rockwood, K., Beattie, B.L., Eastwood, R., Gauthier, S., Tuokko, H., McDowell, I. (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet, Vol. 349, No. 9068 (Jun 21 1997), pp. 1793-1796, issn 0140-6736 (Print) 0140-6736 (Linking).

Gussekloo, J., van Exel, E., de Craen, A.J., Meinders, A.E., Frolich, M., Westendorp, R.G. (2004). Thyroid status, disability and cognitive function, and survival in old age. JAMA, Vol. 292, No. 21 (Dec 1 2004), pp. 2591-2599, issn 1538-3598 (Electronic) 0098-7484 (Linking).

Gussekloo, J., van Exel, E., de Craen, A.J., Meinders, A.E., Frolich, M., Westendorp, R.G. (2006). [Thyroid function, activities of daily living and survival in extreme old age: the 'Leiden 85-plus Study']. Ned Tijdschr Geneeskd, Vol. 150, No. 2 (Jan 14 2006), pp. 90-96, issn 0028-2162 (Print) 0028-2162 (Linking).

Hak, A.E., Pols, H.A., Visser, T.J., Drexhage, H.A., Hofman, A., Witteman, J.C. (2000). Subclinical hypothyroidism is an independent risk factor for atherosclerosis and

myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med, Vol. 132, No. 4 (Feb 15 2000), pp. 270-278, issn 0003-4819 (Print) 0003-4819 (Linking).

Hancock, S.L., Cox, R.S., McDougall, I.R. (1991). Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med, Vol. 325, No. 9 (Aug 29 1991), pp. 599-605, issn 0028-4793 (Print) 0028-4793 (Linking).

Helfand, M. (2004). Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med, Vol. 140, No. 2 (Jan 20 2004), pp. 128-141, issn 1539-3704 (Electronic) 0003-4819 (Linking).

Herholz, K. (2010). Cerebral glucose metabolism in preclinical and prodromal Alzheimer's disease. Expert Rev Neurother, Vol. 10, No. 11 (Nov 2010), pp. 1667-1673, issn 1744-8360 (Electronic) 1473-7175 (Linking).

Hogervorst, E., Huppert, F., Matthews, F.E., Brayne, C. (2008). Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. Psychoneuroendocrinology, Vol. 33, No. 7 (Aug 2008), pp. 1013-1022, issn 0306-4530 (Print) 0306-4530 (Linking).

Hollowell, J.G., Staehling, N.W., Flanders, W.D., Hannon, W.H., Gunter, E.W., Spencer, C.A., Braverman, L.E. (2002). Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab, Vol. 87, No. 2 (Feb 2002), pp. 489-499, issn 0021-972X (Print) 0021-972X (Linking).

Imaizumi, M., Akahoshi, M., Ichimaru, S., Nakashima, E., Hida, A., Soda, M., Usa, T., Ashizawa, K., Yokoyama, N., Maeda, R., Nagataki, S., Eguchi, K. (2004). Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab, Vol. 89, No. 7 (Jul 2004), pp. 3365-3370, issn 0021-972X (Print) 0021-972X (Linking).

Jaeschke, R., Guyatt, G., Gerstein, H., Patterson, C., Molloy, W., Cook, D., Harper, S., Griffith, L., Carbotte, R. (1996). Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? J Gen Intern Med, Vol. 11, No. 12 (Dec 1996), pp. 744-749, issn 0884-8734 (Print) 0884-8734 (Linking).

Kahaly, G.J. (2000). Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid, Vol. 10, No. 8 (Aug 2000), pp. 665-679, issn 1050-7256 (Print) 1050-7256 (Linking).

Kahaly, G.J., Dillmann, W.H. (2005). Thyroid hormone action in the heart. Endocr Rev, Vol. 26, No. 5 (Aug 2005), pp. 704-728, issn 0163-769X (Print) 0163-769X (Linking).

Kalmijn, S., Foley, D., White, L., Burchfiel, C.M., Curb, J.D., Petrovitch, H., Ross, G.W., Havlik, R.J., Launer, L.J. (2000). Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol, Vol. 20, No. 10 (Oct 2000), pp. 2255-2260, issn 1524-4636 (Electronic) 1079-5642 (Linking).

Kanaya, A.M., Harris, F., Volpato, S., Perez-Stable, E.J., Harris, T., Bauer, D.C. (2002). Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Arch Intern Med, Vol. 162, No. 7 (Apr 8 2002), pp. 773-779, issn 0003-9926 (Print) 0003-9926 (Linking).

Karmisholt, J., Andersen, S., Laurberg, P. (2011). Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. Eur J Endocrinol, Vol. 164, No. 3 (Mar 2011), pp. 317-323, issn 1479-683X (Electronic) 0804-4643 (Linking).

Klein, I. (2004). The cardiovascular system in hypothyroidism, In: The Thyroid, A Fundamental and Clinical Text, Bravermann, L.E., Utiger, R.D. pp. 774-80, Ninth Edition, Lippincott Williams and Wilkins, ISBN 0-7817-5047-4(HC), Philadelphia, USA

Klein, I., Danzi, S. (2007). Thyroid disease and the heart. Circulation, Vol. 116, No. 15 (Oct 9 2007), pp. 1725-1735, issn 1524-4539 (Electronic) 0009-7322 (Linking).

Klein, I., Ojamaa, K. (2001). Thyroid hormone and the cardiovascular system. N Engl J Med, Vol. 344, No. 7 (Feb 15 2001), pp. 501-509, issn 0028-4793 (Print) 0028-4793 (Linking).

Kong, W.M., Sheikh, M.H., Lumb, P.J., Naoumova, R.P., Freedman, D.B., Crook, M., Dore, C.J., Finer, N. (2002). A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med, Vol. 112, No. 5 (Apr 1 2002), pp. 348-354, issn 0002-9343 (Print) 0002-9343 (Linking).

Kumar, N., Allen, K.A., Riccardi, D., Bercu, B.B., Cantor, A., Minton, S., Balducci, L., Jacobsen, P.B. (2004). Fatigue, weight gain, lethargy and amenorrhea in breast cancer patients on chemotherapy: is subclinical hypothyroidism the culprit? Breast Cancer Res Treat, Vol. 83, No. 2 (Jan 2004), pp. 149-159, issn 0167-6806 (Print) 0167-6806 (Linking).

Kvetny, J., Heldgaard, P.E., Bladbjerg, E.M., Gram, J. (2004). Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. Clin Endocrinol (Oxf), Vol. 61, No. 2 (Aug 2004), pp. 232-238, issn 0300-0664 (Print) 0300-0664 (Linking).

Ladenson, P.W., Singer, P.A., Ain, K.B., Bagchi, N., Bigos, S.T., Levy, E.G., Smith, S.A., Daniels, G.H., Cohen, H.D. (2000). American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med, Vol. 160, No. 11 (Jun 12 2000), pp. 1573-1575, issn 0003-9926 (Print) 0003-9926 (Linking).

Laurberg, P., Andersen, S., Carle, A., Karmisholt, J., Knudsen, N., Pedersen, I.B. (2011). The TSH upper reference limit: where are we at? Nat Rev Endocrinol, Vol. 7, No. 4 (Apr 2011), pp. 232-239, issn 1759-5037 (Electronic) 1759-5029 (Linking).

Lee, W.Y., Suh, J.Y., Rhee, E.J., Park, J.S., Sung, K.C., Kim, S.W. (2004). Plasma CRP, apolipoprotein A-1, apolipoprotein B and Lpa levels according to thyroid function status. Arch Med Res, Vol. 35, No. 6 (Nov-Dec 2004), pp. 540-545, issn 0188-4409 (Print) 0188-4409 (Linking).

Lekakis, J., Papamichael, C., Alevizaki, M., Piperingos, G., Marafelia, P., Mantzos, J., Stamatelopoulos, S., Koutras, D.A. (1997). Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. Thyroid, Vol. 7, No. 3 (Jun 1997), pp. 411-414, issn 1050-7256 (Print) 1050-7256 (Linking).

Luboshitzky, R., Aviv, A., Herer, P., Lavie, L. (2002). Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid, Vol. 12, No. 5 (May 2002), pp. 421-425, issn 1050-7256 (Print) 1050-7256 (Linking).

Luboshitzky, R., Herer, P. (2004). Cardiovascular risk factors in middle-aged women with subclinical hypothyroidism. Neuro Endocrinol Lett, Vol. 25, No. 4 (Aug 2004), pp. 262-266, issn 0172-780X (Print) 0172-780X (Linking).

Mariotti, S. (2005). Thyroid function and aging: do serum 3,5,3'-triiodothyronine and thyroid-stimulating hormone concentrations give the Janus response? J Clin Endocrinol Metab, Vol. 90, No. 12 (Dec 2005), pp. 6735-6737, issn 0021-972X (Print) 0021-972X (Linking).

Mariotti, S., Barbesino, G., Caturegli, P., Bartalena, L., Sansoni, P., Fagnoni, F., Monti, D., Fagiolo, U., Franceschi, C., Pinchera, A. (1993). Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab, Vol. 77, No. 5 (Nov 1993), pp. 1130-1134, issn 0021-972X (Print) 0021-972X (Linking).

Mariotti, S., Franceschi, C., Cossarizza, A., Pinchera, A. (1995). The aging thyroid. Endocr Rev, Vol. 16, No. 6 (Dec 1995), pp. 686-715, issn 0163-769X (Print) 0163-769X (Linking).

Meier, C., Staub, J.J., Roth, C.B., Guglielmetti, M., Kunz, M., Miserez, A.R., Drewe, J., Huber, P., Herzog, R., Muller, B. (2001). TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab, Vol. 86, No. 10 (Oct 2001), pp. 4860-4866, issn 0021-972X (Print) 0021-972X (Linking).

Mitrou, P., Raptis, S.A., Dimitriadis, G. (2011). Thyroid disease in older people. Maturitas, Vol., No. (Jun 28 2011), pp. issn 1873-4111 (Electronic) 0378-5122 (Linking).

Mohandas, R., Gupta, K.L. (2003). Managing thyroid dysfunction in the elderly. Answers to seven common questions. Postgrad Med, Vol. 113, No. 5 (May 2003), pp. 54-56, 65-58, 100, issn 0032-5481 (Print) 0032-5481 (Linking).

Monzani, F., Caraccio, N., Kozakowa, M., Dardano, A., Vittone, F., Virdis, A., Taddei, S., Palombo, C., Ferrannini, E. (2004). Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. J Clin Endocrinol Metab, Vol. 89, No. 5 (May 2004), pp. 2099-2106, issn 0021-972X (Print) 0021-972X (Linking).

Monzani, F., Dardano, A., Caraccio, N. (2006). Does treating subclinical hypothyroidism improve markers of cardiovascular risk? Treat Endocrinol, Vol. 5, No. 2 2006), pp. 65-81, issn 1175-6349 (Print) 1175-6349 (Linking).

Monzani, F., Del Guerra, P., Caraccio, N., Pruneti, C.A., Pucci, E., Luisi, M., Baschieri, L. (1993). Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. Clin Investig, Vol. 71, No. 5 (May 1993), pp. 367-371, issn 0941-0198 (Print) 0941-0198 (Linking).

Muller, B., Tsakiris, D.A., Roth, C.B., Guglielmetti, M., Staub, J.J., Marbet, G.A. (2001). Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. Eur J Clin Invest, Vol. 31, No. 2 (Feb 2001), pp. 131-137, issn 0014-2972 (Print) 0014-2972 (Linking).

Nystrom, E., Caidahl, K., Fager, G., Wikkelso, C., Lundberg, P.A., Lindstedt, G. (1988). A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. Clin Endocrinol (Oxf), Vol. 29, No. 1 (Jul 1988), pp. 63-75, issn 0300-0664 (Print) 0300-0664 (Linking).

Ochs, N., Auer, R., Bauer, D.C., Nanchen, D., Gussekloo, J., Cornuz, J., Rodondi, N. (2008). Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med, Vol. 148, No. 11 (Jun 3 2008), pp. 832-845, issn 1539-3704 (Electronic) 0003-4819 (Linking).

Ojamaa, K., Klemperer, J.D., Klein, I. (1996). Acute effects of thyroid hormone on vascular smooth muscle. Thyroid, Vol. 6, No. 5 (Oct 1996), pp. 505-512, issn 1050-7256 (Print) 1050-7256 (Linking).

Olsen, K.J. (1978). Scintigraphic estimation of thyroid volume and dose distribution at treatment with 131I. Acta Radiol Oncol Radiat Phys Biol, Vol. 17, No. 1 1978), pp. 74-80, issn 0348-5196 (Print) 0348-5196 (Linking).

Ooka, H., Fujita, S., Yoshimoto, E. (1983). Pituitary-thyroid activity and longevity in neonatally thyroxine-treated rats. Mech Ageing Dev, Vol. 22, No. 2 (Jun 1983), pp. 113-120, issn 0047-6374 (Print) 0047-6374 (Linking).

Osterweil, D., Syndulko, K., Cohen, S.N., Pettler-Jennings, P.D., Hershman, J.M., Cummings, J.L., Tourtellotte, W.W., Solomon, D.H. (1992). Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc, Vol. 40, No. 4 (Apr 1992), pp. 325-335, issn 0002-8614 (Print) 0002-8614 (Linking).

Palmieri, E.A., Fazio, S., Lombardi, G., Biondi, B. (2004). Subclinical hypothyroidism and cardiovascular risk: a reason to treat? Treat Endocrinol, Vol. 3, No. 4 2004), pp. 233-244, issn 1175-6349 (Print) 1175-6349 (Linking).

Patel, J., Landers, K., Li, H., Mortimer, R.H., Richard, K. (2011). Thyroid hormones and fetal neurological development. J Endocrinol, Vol. 209, No. 1 (Apr 2011), pp. 1-8, issn 1479-6805 (Electronic) 0022-0795 (Linking).

Prinz, P.N., Scanlan, J.M., Vitaliano, P.P., Moe, K.E., Borson, S., Toivola, B., Merriam, G.R., Larsen, L.H., Reed, H.L. (1999). Thyroid hormones: positive relationships with cognition in healthy, euthyroid older men. J Gerontol A Biol Sci Med Sci, Vol. 54, No. 3 (Mar 1999), pp. M111-116, issn 1079-5006 (Print) 1079-5006 (Linking).

Razvi, S., Ingoe, L., Keeka, G., Oates, C., McMillan, C., Weaver, J.U. (2007). The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab, Vol. 92, No. 5 (May 2007), pp. 1715-1723, issn 0021-972X (Print) 0021-972X (Linking).

Razvi, S., Shakoor, A., Vanderpump, M., Weaver, J.U., Pearce, S.H. (2008). The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab, Vol. 93, No. 8 (Aug 2008), pp. 2998-3007, issn 0021-972X (Print) 0021-972X (Linking).

Razvi, S., Weaver, J.U., Vanderpump, M.P., Pearce, S.H. (2010). The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab, Vol. 95, No. 4 (Apr 2010), pp. 1734-1740, issn 1945-7197 (Electronic) 0021-972X (Linking).

Rivolta, G., Cerutti, R., Colombo, R., Miano, G., Dionisio, P., Grossi, E. (1999). Prevalence of subclinical hypothyroidism in a population living in the Milan metropolitan area. J Endocrinol Invest, Vol. 22, No. 9 (Oct 1999), pp. 693-697, issn 0391-4097 (Print) 0391-4097 (Linking).

Roberts, L.M., Pattison, H., Roalfe, A., Franklyn, J., Wilson, S., Hobbs, F.D., Parle, J.V. (2006). Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Intern Med, Vol. 145, No. 8 (Oct 17 2006), pp. 573-581, issn 1539-3704 (Electronic) 0003-4819 (Linking).

Rodondi, N., Aujesky, D., Vittinghoff, E., Cornuz, J., Bauer, D.C. (2006). Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. Am J Med, Vol. 119, No. 7 (Jul 2006), pp. 541-551, issn 1555-7162 (Electronic) 0002-9343 (Linking).

Rodondi, N., den Elzen, W.P., Bauer, D.C., Cappola, A.R., Razvi, S., Walsh, J.P., Asvold, B.O., Iervasi, G., Imaizumi, M., Collet, T.H., Bremner, A., Maisonneuve, P., Sgarbi, J.A., Khaw, K.T., Vanderpump, M.P., Newman, A.B., Cornuz, J., Franklyn, J.A., Westendorp, R.G., Vittinghoff, E., Gussekloo, J. (2010). Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA, Vol. 304, No. 12 (Sep 22 2010), pp. 1365-1374, issn 1538-3598 (Electronic) 0098-7484 (Linking).

Ross, D.S., (2004). subclinical hypothyroidism, in: The thyroid, A Fundamental and Clinical Text. Lippincott Williams and Wilkins, isbn 0-7817-5047-4 (HC), Philadelphia.

Rozing, M.P., Houwing-Duistermaat, J.J., Slagboom, P.E., Beekman, M., Frolich, M., de Craen, A.J., Westendorp, R.G., van Heemst, D. (2010). Familial longevity is associated with decreased thyroid function. J Clin Endocrinol Metab, Vol. 95, No. 11 (Nov 2010), pp. 4979-4984, issn 1945-7197 (Electronic) 0021-972X (Linking).

Samuels, M.H. (1998). Subclinical thyroid disease in the elderly. Thyroid, Vol. 8, No. 9 (Sep 1998), pp. 803-813, issn 1050-7256 (Print) 1050-7256 (Linking).

Sawin, C.T., Castelli, W.P., Hershman, J.M., McNamara, P., Bacharach, P. (1985). The aging thyroid. Thyroid deficiency in the Framingham Study. Arch Intern Med, Vol. 145, No. 8 (Aug 1985), pp. 1386-1388, issn 0003-9926 (Print) 0003-9926 (Linking).

Sawin, C.T., Chopra, D., Azizi, F., Mannix, J.E., Bacharach, P. (1979). The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. JAMA, Vol. 242, No. 3 (Jul 20 1979), pp. 247-250, issn 0098-7484 (Print) 0098-7484 (Linking).

Shih, C.H., Chen, S.L., Yen, C.C., Huang, Y.H., Chen, C.D., Lee, Y.S., Lin, K.H. (2004). Thyroid hormone receptor-dependent transcriptional regulation of fibrinogen and coagulation proteins. Endocrinology, Vol. 145, No. 6 (Jun 2004), pp. 2804-2814, issn 0013-7227 (Print) 0013-7227 (Linking).

Singh, S., Duggal, J., Molnar, J., Maldonado, F., Barsano, C.P., Arora, R. (2008). Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. Int J Cardiol, Vol. 125, No. 1 (Mar 28 2008), pp. 41-48, issn 1874-1754 (Electronic) 0167-5273 (Linking).

Spencer, C.A., Schwarzbein, D., Guttler, R.B., LoPresti, J.S., Nicoloff, J.T. (1993). Thyrotropin (TSH)-releasing hormone stimulation test responses employing third and fourth generation TSH assays. J Clin Endocrinol Metab, Vol. 76, No. 2 (Feb 1993), pp. 494-498, issn 0021-972X (Print) 0021-972X (Linking).

Squizzato, A., Romualdi, E., Piantanida, E., Gerdes, V.E., Buller, H.R., Tanda, M., Bartalena, L., Venco, A., Ageno, W. (2007). Subclinical hypothyroidism and deep venous thrombosis. A pilot cross-sectional study. Thromb Haemost, Vol. 97, No. 5 (May 2007), pp. 803-806, issn 0340-6245 (Print) 0340-6245 (Linking).

St John, J.A., Henderson, V.W., Gatto, N.M., McCleary, C.A., Spencer, C.A., Hodis, H.N., Mack, W.J. (2009). Mildly elevated TSH and cognition in middle-aged and older adults. Thyroid, Vol. 19, No. 2 (Feb 2009), pp. 111-117, issn 1557-9077 (Electronic) 1050-7256 (Linking).

Staub, J.J., Althaus, B.U., Engler, H., Ryff, A.S., Trabucco, P., Marquardt, K., Burckhardt, D., Girard, J., Weintraub, B.D. (1992). Spectrum of subclinical and overt hypothyroidism:

effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med, Vol. 92, No. 6 (Jun 1992), pp. 631-642, issn 0002-9343 (Print) 0002-9343 (Linking).

Surks, M.I., Hollowell, J.G. (2007). Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab, Vol. 92, No. 12 (Dec 2007), pp. 4575-4582, issn 0021-972X (Print) 0021-972X (Linking).

Surks, M.I., Ocampo, E. (1996). Subclinical thyroid disease. Am J Med, Vol. 100, No. 2 (Feb 1996), pp. 217-223, issn 0002-9343 (Print) 0002-9343 (Linking).

Surks, M.I., Ortiz, E., Daniels, G.H., Sawin, C.T., Col, N.F., Cobin, R.H., Franklyn, J.A., Hershman, J.M., Burman, K.D., Denke, M.A., Gorman, C., Cooper, R.S., Weissman, N.J. (2004). Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA, Vol. 291, No. 2 (Jan 14 2004), pp. 228-238, issn 1538-3598 (Electronic) 0098-7484 (Linking).

Szabolcs, I., Podoba, J., Feldkamp, J., Dohan, O., Farkas, I., Sajgo, M., Takats, K.I., Goth, M., Kovacs, L., Kressinszky, K., Hnilica, P., Szilagyi, G. (1997). Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis and abundant iodine intake. Clin Endocrinol (Oxf), Vol. 47, No. 1 (Jul 1997), pp. 87-92, issn 0300-0664 (Print) 0300-0664 (Linking).

Taddei, S., Caraccio, N., Virdis, A., Dardano, A., Versari, D., Ghiadoni, L., Ferrannini, E., Salvetti, A., Monzani, F. (2006). Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. J Clin Endocrinol Metab, Vol. 91, No. 12 (Dec 2006), pp. 5076-5082, issn 0021-972X (Print) 0021-972X (Linking).

Taddei, S., Caraccio, N., Virdis, A., Dardano, A., Versari, D., Ghiadoni, L., Salvetti, A., Ferrannini, E., Monzani, F. (2003). Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab, Vol. 88, No. 8 (Aug 2003), pp. 3731-3737, issn 0021-972X (Print) 0021-972X (Linking).

Tan, Z.S., Beiser, A., Vasan, R.S., Au, R., Auerbach, S., Kiel, D.P., Wolf, P.A., Seshadri, S. (2008). Thyroid function and the risk of Alzheimer disease: the Framingham Study. Arch Intern Med, Vol. 168, No. 14 (Jul 28 2008), pp. 1514-1520, issn 1538-3679 (Electronic) 0003-9926 (Linking).

Tappy, L., Randin, J.P., Schwed, P., Wertheimer, J., Lemarchand-Beraud, T. (1987). Prevalence of thyroid disorders in psychogeriatric inpatients. A possible relationship of hypothyroidism with neurotic depression but not with dementia. J Am Geriatr Soc, Vol. 35, No. 6 (Jun 1987), pp. 526-531, issn 0002-8614 (Print) 0002-8614 (Linking).

Tunbridge, W.M., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Evans, J.G., Young, E., Bird, T., Smith, P.A. (1977). The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf), Vol. 7, No. 6 (Dec 1977), pp. 481-493, issn 0300-0664 (Print) 0300-0664 (Linking).

Turemen, E.E., Cetinarslan, B., Sahin, T., Canturk, Z., Tarkun, I. (2011). Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. Endocr J, Vol. 58, No. 5 2011), pp. 349-354, issn 1348-4540 (Electronic) 0918-8959 (Linking).

van den Beld, A.W., Visser, T.J., Feelders, R.A., Grobbee, D.E., Lamberts, S.W. (2005). Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. J Clin Endocrinol Metab, Vol. 90, No. 12 (Dec 2005), pp. 6403-6409, issn 0021-972X (Print) 0021-972X (Linking).

Vanderpump, M.P., Tunbridge, W.M., French, J.M., Appleton, D., Bates, D., Clark, F., Grimley Evans, J., Hasan, D.M., Rodgers, H., Tunbridge, F., et al. (1995). The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf), Vol. 43, No. 1 (Jul 1995), pp. 55-68, issn 0300-0664 (Print) 0300-0664 (Linking).

Villar, H.C., Saconato, H., Valente, O., Atallah, A.N. (2007). Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev, Vol., No. 3 2007), pp. CD003419, issn 1469-493X (Electronic) 1361-6137 (Linking).

Volpato, S., Guralnik, J.M., Fried, L.P., Remaley, A.T., Cappola, A.R., Launer, L.J. (2002). Serum thyroxine level and cognitive decline in euthyroid older women. Neurology, Vol. 58, No. 7 (Apr 9 2002), pp. 1055-1061, issn 0028-3878 (Print) 0028-3878 (Linking).

Walsh, J.P., Bremner, A.P., Bulsara, M.K., O'Leary, P., Leedman, P.J., Feddema, P., Michelangeli, V. (2005). Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol (Oxf), Vol. 63, No. 6 (Dec 2005), pp. 670-675, issn 0300-0664 (Print) 0300-0664 (Linking).

Walton, K.W., Campbell, D.A., Tonks, E.L. (1965). The significance of alterations in serum lipids in thyroid dysfunction. I. The relation between serum lipoproteins, carotenoids and vitamin A in hypothyroidism and thyrotoxicosis. Clin Sci, Vol. 29, No. 2 (Oct 1965), pp. 199-215, issn 0009-9287 (Print) 0009-9287 (Linking).

Wang, C., Crapo, L.M. (1997). The epidemiology of thyroid disease and implications for screening. Endocrinol Metab Clin North Am, Vol. 26, No. 1 (Mar 1997), pp. 189-218, issn 0889-8529 (Print) 0889-8529 (Linking).

Yamamoto, N., Ishizawa, K., Ishikawa, M., Yamanaka, G., Yamanaka, T., Murakami, S., Hiraiwa, T., Okumiya, K., Ishine, M., Matsubayashi, K., Otsuka, K. (2012). Cognitive function with subclinical hypothyroidism in elderly people without dementia: One year follow up. Geriatr Gerontol Int, Vol. 12, No. 1 (Jan 2012), pp. 164-165, issn 1447-0594 (Electronic) 1447-0594 (Linking).

Zoeller, R.T., Rovet, J. (2004). Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J Neuroendocrinol, Vol. 16, No. 10 (Oct 2004), pp. 809-818, issn 0953-8194 (Print) 0953-8194 (Linking).

Zulewski, H., Muller, B., Exer, P., Miserez, A.R., Staub, J.J. (1997). Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab, Vol. 82, No. 3 (Mar 1997), pp. 771-776, issn 0021-972X (Print) 0021-972X (Linking).