

# 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

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## Abstract

**Background:** several studies suggest that a decreased thyroid activity might be favourable in oldest-old subjects and that subclinical thyroid hyperfunction may be detrimental.

**Objectives:** to verify whether declining levels of circulating thyroid hormones may contribute to longevity.

**Design:** cross-sectional observational study.

**Setting:** all subjects were born in Calabria (southern Italy) and their ancestry in the region was ascertained up to the grandparents.

**Subjects:** six hundred and four home-dwelling subjects (301 females, 303 males), divided into three groups: 278 individuals 60–85 years old; 179 children or nieces/nephews of centenarians who are 60–85 years old; 147 individuals older than 85 years.

**Methods:** thyroid function parameters were measured in the frame of a comprehensive geriatric assessment.

**Results:** FT3 and FT4 levels were negatively associated with age. Lower levels of FT3, FT4 and TSH were found in centenarians' children and nieces/nephews with respect to age-matched controls. Indeed, being a relative of centenarians qualified as an independent correlate of thyroid parameters.

**Conclusions:** age-related subtle thyroid hypofunction (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) appears to be related to longevity.

**Keywords:** ageing, thyroid, survival, free-triiodothyronine, elderly

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## Introduction

Several changes in thyroid function are frequently observed in the elderly [1, 2]. An increased prevalence of serum thyroid antibodies and clinical and subclinical hypothyroidism has been consistently reported, up to a prevalence of 20% in women older than 60–65 years [3]. The prevalence of subclinical hyperthyroidism is also increased in aged subjects of both sexes, affecting 1–1.5% of the general

population in iodine-sufficient areas [3] and up to 7–8% in iodine-deficient areas [4]. Moreover, the coexistence of several age-associated diseases may account for serum thyroid hormone and thyroid-stimulating hormone (TSH) abnormalities characteristic of the non-thyroidal illness (NTI) syndrome [2]. However, an age-dependent decline of thyroid function, at least partially independent from associated NTI, has been documented, particularly in the ninth decade of life [2, 5].

Whether and to what extent this phenomenon represents a physiologic adaptive mechanism to different metabolic needs, or a subtle metabolic change contributing to the ageing process, remains unclear [6]. Evidences raised in the last few years support the hypothesis that some degree of decreased thyroid activity might have favourable effects in the oldest-old subjects, whereas either clinical or subclinical thyroid hyperfunction may be detrimental [7, 8]. However, the issue of whether such an age-related decrease in thyroid activity might represent an adaptive mechanism occurring in the latest decades of life or might onset in middle-aged subjects, thus contributing to favour longevity, is still to be settled. Therefore, we aimed at investigating changes in thyroid hormone status in a group of subjects aged from 60 to 105 years. In particular, we tried to verify: (i) whether circulating levels of thyroid hormones reduce with ageing and (ii) whether their reduction is associated with extreme longevity.

## Methods

### Sample

Participants to the study were 604 subjects (303 males and 301 females), divided into three groups.

The first group is represented by 278 individuals aged between 60 and 85 (CG 60–85) not having long-lived parents; the second group is composed of 179 individuals aged between 60 and 85 (CR 60–85) who are children or nieces/nephews of centenarians; finally, the third group is represented by 147 individuals aged more than 85 (85+). The absence of children of centenarians in the CG 60–85 group was ascertained by asking about parent's age at death to all the subjects recruited and by double checking on the lists of Calabrian centenarians obtained from municipalities of this region. All the subjects were born in Calabria (southern Italy) and their ancestry in the region had been ascertained up to the grandparents' generation. The sample was recruited in the frame of different recruitment campaigns carried out by the research group between 2002 and 2007. Subjects were identified by screening of population registers in different municipalities distributed across the entire Calabria region. Subjects who were eligible for age (>60 years) were contacted and asked for participating in the study. Centenarians, their children and nieces/nephews were collected in the frame of the European Challenge of Healthy Aging (ECHA) Project [9]. Study design and questionnaires used are freely accessible at the following web site: <http://biologia.unical.it/echa/results.htm>.

For the present study, 65 subjects were excluded from the analysis because of TSH values out of range (44 subjects showed TSH < 0.27  $\mu$ IU/ml; 21 subjects had TSH > 4.20  $\mu$ IU/ml), leaving 539 subjects for the analysis. All the subjects had given written informed consent to participate in the study. The study protocol was approved by the ethical committee at the University of Calabria, Italy.

### Measurement of thyroid function parameters

Plasma was obtained from all subjects by centrifugation (at 3000 r.p.m. for 20 min at room temperature) of whole blood samples collected after an overnight fasting, and it was stored at  $-80^{\circ}\text{C}$  until the assay. Free-triiodothyronine (FT3), free-thyroxine (FT4) and TSH were measured by ElectroChemiLuminescence ImmunoAssay (ECLIA) using Elecsys 2010 analyzer (Hitachi Ltd, Tokyo, Japan). The normal range was 2.0–4.4 pg/ml for FT3, 0.93–1.70 ng/dl for FT4 and 0.27–4.20  $\mu$ IU/ml for TSH. The intra-assay and inter-assay coefficients of variation were 3.3 and 5.1% for FT3, 1.6 and 3.5% for FT4 and 8.6 and 8.7% for TSH, respectively. The lower limit of sensitivity was 0.26 pg/ml for FT3, 0.023 ng/dl for FT4, and 0.005  $\mu$ IU/ml for TSH.

### Analytic approach and statistical analysis

Comparisons within the three sample groups were performed by contingency tables with chi-square test used for categorical variables and ANOVA test for continuous ones followed by multiple comparison test (Dunnett's test). Demographic and clinical features were compared among the groups previously defined. Variables considered in the analyses were: cognitive function, as measured by age- and education-adjusted mini-mental state examination (MMSE) score [10]; depressive symptoms, as ascertained on the basis of the short form (15 items) of the Geriatric Depression Scale (GDS) [11]; functional activity, as assessed by using a modification of the Katz' index of ADL [12]. The assessment was based on what the subject was able to do at the time of the visit. Health status was ascertained by medical visit carried out by a geriatrician, who also conducted a structured interview including questions on common diseases occurred in the past. The number of diagnoses was also calculated and considered as an overall index of comorbidity.

Multiple regression was used to investigate the relationship between thyroid hormone levels and age and to test for differences between the mean thyroid hormone levels of the groups while adjusting for age. The thyroid measures were used as dependent variables, age was used as a covariate and group as a factor. The interaction between age and group was included in order to test whether the slopes of the regression lines were the same. Other possible confounders, and their interactions with group, were also included in the regression using a forward stepwise method and were retained in the model only if they proved to be significant. A *P*-value less than 0.05 was regarded as indicating statistical significance throughout.

All statistical procedures were performed using SPSS 15.0 statistical software package (SPSS Inc, Chicago, IL, USA).

## Results

Demographic and clinical characteristics of subjects divided according to group membership are reported in Table 1. Gender distribution was similar in the three groups,

**Table 1.** Demographic and clinical characteristics of the three sub-samples

	CG 60–85, n = 278	85+, n = 147	CR 60–85, n = 179	P-value
Males	147 (52.9%)	74 (50.3%)	82 (45.8%)	0.337
MMSE ≤ 23	87 (32.3%)	130 (89.0%)	74 (41.3%)	<0.001
GDS > 5	95 (36.5%)	50 (42.4%)	50 (28.6%)	0.044
No ADL disability	42 (15.5%)	115 (78.8%)	1 (0.6%)	<0.001
FT3 (pg/ml)	3.35 (0.64)	2.55 (0.59)	3.19 (0.65)	<0.001*
Free thyroxine (ng/dl)	1.32 (0.26)	1.25 (0.23)	1.21 (0.21)	<0.001*
TSH (μU/ml)	1.39 (0.86)	1.54 (0.89)	1.16 (0.64)	<0.001*
Diabetes	53 (19.6%)	15 (10.3%)	26 (14.6%)	0.039
Hypertension	150 (55.6%)	55 (37.7%)	89 (49.7%)	0.002
Angina pectoris	24 (8.9%)	12 (8.3%)	15 (8.5%)	0.975
Heart failure	42 (15.6%)	45 (31.7%)	13 (7.4%)	<0.001
Arrhythmias	63 (23.4%)	28 (19.3%)	15 (8.4%)	<0.001
Asthma	26 (9.7%)	20 (13.9%)	10 (5.6%)	0.043
COP disease	84 (31.2%)	67 (46.5%)	25 (14.0%)	<0.001
Arthritis	195 (72.5%)	106 (73.6%)	144 (81.4%)	0.088
Migraine	60 (22.3%)	13 (9.0%)	15 (8.5%)	<0.001
Osteoporosis	67 (24.9%)	22 (15.3%)	34 (19.3%)	0.060
Gastric ulcer	67 (24.9%)	27 (19.3%)	34 (19.3%)	0.263
Stroke	21 (7.9%)	11 (8.5%)	3 (1.9%)	0.024
Heart attack	27 (10.2%)	6 (4.6%)	3 (1.9%)	0.002
Cancer	11 (4.1%)	7 (5.3%)	13 (8.1%)	0.215
Pneumonia	19 (7.1%)	7 (5.4%)	5 (3.1%)	0.210
Number of diagnoses	3.3 ± 2.03	3.1 ± 2.00	2.4 ± 1.61	<0.001*

P-values refer to the chi-square test. Abbreviations: CG 60–85, control group; 85+, 85-plus subjects; CR 60–85, centenarians' relatives.

Dunnnett's multiple comparison test: FT3: CR 60–85 versus CG 60–85,  $P = 0.017$ ; 85+ versus CG 60–85,  $P < 0.001$ ; Free thyroxine: CR 60–85 versus CG 60–85,  $P < 0.001$ ; 85+ versus CG 60–85,  $P = 0.007$ ; TSH: CR 60–85 versus CG 60–85,  $P = 0.009$ ; 85+ versus CG 60–85,  $P = 0.124$ ; number of diagnoses: CR 60–85 versus CG 60–85,  $P < 0.001$ ; 85+ versus CG 60–85,  $P = 0.616$ .

\*P-values refer to the ANOVA test.

whereas cognitive impairment, physical dependency and depressive symptoms were more frequent among oldest-old subjects, as well as heart failure and chronic obstructive pulmonary (COP) disease. On the contrary, diabetes, hypertension, osteoporosis and migraine were more frequent among subjects aged less than 85. Noteworthy, children or nieces/nephews of centenarians showed less disability, as well as a lower incidence of cardiovascular diseases (heart failure, arrhythmias, stroke, heart attack), migraine and COP diseases with respect to the age-matched controls. This group also showed a lower number of diagnosed diseases in comparison with their age peers not belonging to centenarians' families.

The mean value of FT3 observed in the whole studied population was 3.11 pg/ml (SD: 0.71, range 0.94–5.09). The corresponding figures for FT4 and TSH were 1.27 ng/dl (SD: 0.24, range 0.78–2.00) and 1.36 μU/ml (SD: 0.82, range 0.27–4.08), respectively.

Table 2 reports the results of the multiple regression analyses of thyroid hormone levels on age and group membership (using two indicator variables) and their interactions. From these models, we found that age was significantly associated with a decrease in FT3 and FT4 levels ( $\beta = -0.035$ ,  $P < 0.001$ ;  $\beta = -0.005$ ,  $P = 0.010$ ,

**Table 2.** Multiple regression models of thyroid hormone levels on age and group membership

Variable	Coefficient ( $\beta$ )	SE	t	P-value	Lower 95% CI	Upper 95% CI
<b>FT3</b>						
Intercept	5.957	0.482	12.349	<0.001	5.010	6.905
Age	-0.035	0.007	-5.421	<0.001	-0.048	-0.022
Group = 85+	-2.018	1.126	-1.792	0.074	-4.230	0.193
Group = CR	-1.602	0.793	-2.020	0.044	-3.159	-0.045
Age * 85+	0.021	0.012	1.670	0.095	-0.004	0.045
Age * CR	0.018	0.011	1.649	0.100	-0.004	0.040
<b>Free thyroxine (FT4)</b>						
Intercept	1.731	0.158	10.983	<0.001	1.422	2.041
Age	-0.005	0.002	-2.589	0.010	-0.010	-0.001
Group = 85+	0.049	0.052	0.943	0.346	-0.053	0.152
Group = CR	-0.728	0.288	-2.528	0.012	-1.293	-0.162
Age * CR	0.008	0.004	2.086	0.037	0.000	0.016
<b>TSH</b>						
Intercept	1.564	0.463	3.375	0.001	0.654	2.475
Age	-0.002	0.006	-0.385	0.700	-0.015	0.010
Group = 85+	0.204	0.160	1.280	0.201	-0.109	0.517
Group = CR	-0.234	0.083	-2.809	0.005	-0.397	-0.070

Asterisk indicates the interaction terms.

respectively) but not with TSH ( $\beta = -0.002$ ,  $P = 0.700$ ). However, for FT4, the age-related decline in values was significantly lower in the control group than in the CR group ( $\beta = 0.008$ ,  $P = 0.037$ ). Overall, children or nieces/nephews of centenarians had significantly lower FT3 ( $\beta = -1.602$ ,  $P = 0.044$ ), FT4 ( $\beta = -0.728$ ,  $P < 0.012$ ) and TSH levels ( $\beta = -0.234$ ,  $P = 0.005$ ) than the age-matched subjects who were not children or nieces/nephews of centenarians.

After adjusting for the possible confounders, the significance of group membership effects on hormone levels resulted to be still statistically significant only in children or nieces/nephews of centenarians group (see Supplementary data available in *Age and Ageing* online). In fact, after adjusting for confounders, children or nieces/nephews of centenarians had significantly lower value for FT3 ( $\beta = -0.346$ ,  $P < 0.001$ ) and FT4 ( $\beta = -0.678$ ,  $P = 0.027$ ) than the age-matched subjects who were not children or nieces/nephews of centenarians. In both these models, only the interaction between 85+ group membership and ADL turned out to be significant. No confounders and relevant interactions were added into the TSH regression model by the stepwise procedure.

## Discussion

Changes in thyroid hormones metabolism observed in elderly patients with NTI have been formerly interpreted as a finalistic mechanism leading to a reduction in catabolic processes and oxygen consumption in the course of chronic diseases [13, 14]. However, ageing *per se* may be associated with a resetting of thyroid function which resembles the NTI syndrome [2, 5]. Indeed, a significant age-related reduction in serum total and free T3 levels has been demonstrated, particularly in non-agenarians, whereas serum total and free T4 concentrations did not show any correlation with age [2]. These

findings suggest that age-related reduction of thyroid hormones might occur at advanced ages as a mechanism resetting metabolic processes to a lower level of oxygen consumption. The observation that ageing process and hypothyroidism share an important pathophysiological mechanism (i.e. in both conditions, basal metabolic rate decreases) [15] seems to support this hypothesis. Pathophysiological mechanisms involved in the observed changes in thyroid function include an age-related decline of hepatic 5'-deiodinase activity [16] and a reduction in TSH secretion from the pituitary gland [2, 17]. However, it has recently been demonstrated that common genetic variations in deiodinase 1 (*DIO1*) gene can alter deiodinase function, resulting in an alteration in the balance of circulating FT3 to FT4 [18]. This finding could provide a valuable tool to evaluate genetic factors affecting thyroid hormone levels and age-associated diseases in the course of the ageing process, and the study of the *DIO1* expression in elderly subjects warrants further investigation.

Our results confirm the existence of an age-related decrease in the circulating FT3 levels [2]. On the other hand, we demonstrated for the first time that the negative dependence between age and FT3 levels is specifically observed in the group of subjects aged 60–85 but not in the group of people older than 85 years. In 85+ subjects, however, we found that the levels of circulating thyroid hormones are significantly lower than those in younger subjects. This finding may indicate that the decrease in circulating FT3 might specifically occur before reaching the ninth decade of life to adapt metabolic processes and to favour longevity.

A different, complementary, perspective may be given by the analysis of the group of 60–85 years subjects who are children or nieces/nephews of centenarians (CR group). In line with the life-long sustained survival advantage of centenarians' relatives, well documented in the literature [19], we observed that children or nieces/nephews of centenarians have less disability, as well as a low prevalence of cardiovascular diseases, migraine and COP diseases with respect to the age-matched controls. On the other hand, we found that of centenarians' relatives have reduced FT3, FT4 and TSH levels when compared with age-matched subjects who are not relatives of centenarians. The finding that CR group is characterized by less comorbidity and low levels of thyroid parameters with respect to CG group seems to deny the interpretation that observed differences in thyroid function are due simply to chronic NTI and raise the possibility that low levels of thyroid parameters may be partly genetically determined. In keeping with such a hypothesis, the age-related decrease of FT3 could also be interpreted as a demographic selection favouring the subjects with low levels of thyroid hormones. Such an interpretation seems to be in agreement with a recent observation that middle-aged offspring of nonagenarian siblings have low circulating concentrations of FT3 with respect to their middle-aged partners [20]. Further supporting this view is the knowledge that heritability may contribute to determine not only TSH levels [21, 22], but somewhat FT4 and FT3 levels [22].

The findings from the present study have important interpretative implications. Indeed, our results indicate that age-associated changes in thyroid function might represent a physiological mechanism directly contributing to the ageing process through a resetting of the hormonal milieu which may favour successful ageing and longevity, rather than an adaptation to the need of reducing the catabolic processes and oxygen consumption. Such a conceptual framework is in agreement with previous studies showing that elderly subjects with low serum FT3 and FT4 concentrations had longer survival, especially in the presence of normal reverse T3 concentrations [7]. If confirmed, this interpretation would implicate that subtle hypothyroid status should be considered as a marker of robustness, while either clinical or subclinical hyperthyroidism, which are known to exert a detrimental effect on survival, physical performance, cognitive status and bone mineral content [8, 23–25], should find a place among the markers of frailty.

Limitations of this study should be considered. First, the cross-sectional design of our study does not allow us to assess prospectively the impact of thyroid hormone status on survival. Although this issue deserves further investigation, results obtained in relatives of centenarians are suggestive of a thyroid resetting which could favour longevity. Second, as only patients with thyroid hormone values within the normal range were included in the analysis, the current study is unable to clarify whether subclinical hypothyroidism also represents a marker of longevity or it rather would benefit from replacement therapy. However, there is lack of sufficient evidence to recommend routine treatment for patients with subclinical hypothyroidism [26], and this issue warrants further investigation. Finally, being reverse T3 not measured, subjects carrying a catabolic state characterized by low FT3 and high reverse T3, which are known to be at risk of functional decline [7], cannot be identified in our study.

In conclusion, our study shows that healthy ageing and longevity are favoured by low levels of thyroid hormones. Familiarity seems to have a role in determining low levels of these hormones. In addition, ageing showed to be associated with relevant changes in thyroid function. Age-related subtle thyroid hypofunction may onset between the sixth and the eighth decade of life as a finalistic mechanism favouring successful longevity.

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## Key points

- FT3 levels in old subjects are negatively associated with age.
  - Relatives of centenarians who are 60–85 years old have significantly reduced FT3, FT4 and TSH levels than age-matched controls.
  - Down-regulation of thyroid hormones, due to either genetic predisposition or resetting of thyroid function, favours longevity.
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## Conflicts of interest

None declared.

## Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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