

# High androgen levels protect against hypothyroidism

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## Key words

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## Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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## Abstract

**Introduction.** Hypothyroidism is a common disorder, appearing mainly in women although less frequently found in women with polycystic ovary syndrome (PCOS). The objective was to test the hypothesis that hyperandrogenism might protect against hypothyroidism. **Material and methods.** The data from three prospective follow-up studies (up to 21 years) and one register study were compared: women with PCOS (Rotterdam criteria),  $n = 25$ , women with Turner syndrome,  $n = 217$ , a random population sample of women,  $n = 315$ , and men,  $n = 95$  (the WHO MONICA study). Findings were to be verified or rejected in all females,  $n = 553\ 716$ , from the same region. The proportion of hypothyroidism was calculated and thyroid peroxidase antibodies (TPO) in serum were measured. **Results.** Hypothyroidism at  $>50$  years of age was found in 8% of women with PCOS, 4% in men (PCOS vs. men; ns), 43% of women with Turner syndrome, irrespective of karyotype ( $p < 0.001$  vs. PCOS), and in 17% of postmenopausal women in the population ( $p < 0.01$  vs. PCOS). Elevated TPO were similar in PCOS and women and men in the population but higher in Turner syndrome. Hypothyroidism increased with age in all groups except PCOS women and men. In the register study, hypothyroidism was less common in women with PCOS  $>25$  years (5.5%) than in women without PCOS (6.8%) from the same region ( $p < 0.01$ ). **Conclusions.** Hypothyroidism was less frequently seen in women with PCOS and in men compared with women in the general population and among women with Turner syndrome. This was not explained by altered autoimmunity or the Y-chromosome. Androgens seem to protect against hypothyroidism.

**Abbreviations:** FAI, free androgen index; HT, hormone therapy; PCOS, polycystic ovary syndrome; S, serum; SHBG, sexual hormone-binding globulin; T4, thyroxine; TPO, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone; WHO MONICA, World Health Organization monitoring of trends and determinants for cardiovascular disease.

## Introduction

Subclinical hypothyroidism is a common disorder affecting ~7.5% of females and ~3% of males in the general population (1). Overt hypothyroidism develops at a rate of 5–10% per year (1). Hypothyroidism is thought to

increase the risk of cardiovascular events (2–5), via hyperlipidemia (6,7) and direct effects on the heart (8). For this reason, further research on the pathophysiology of hypothyroidism is important. The causes of hypothyroidism could be central (consequence of various disorders affecting the pituitary gland or the hypothalamus, or both), but primary hypothyroidism is a 1000 times more

common (9). One reason for the increased prevalence of hypothyroidism in women compared with men is that autoimmune disorders are more common in women.

Polycystic ovary syndrome (PCOS), characterized by hyperandrogenism, oligo/amenorrhea and/or polycystic ovaries, is the most common endocrine disorder in women of reproductive age (10,11). In recent studies, hyperandrogenism in postmenopausal women with PCOS has been shown to be persistent (12,13). A decreased prevalence of hypothyroidism in PCOS women (8%) compared with a random population sample of age-matched controls (34%) ( $p < 0.05$ ) has been found incidentally (12).

Hypothyroidism is common (25%) in women with Turner syndrome (14) (caused by a sex chromosome aberration; monosomy 45X, mosaicism 45X/46XX, iso-, ring- or Y- chromosome). Women with Turner syndrome have lower levels of androgens and lack, or have very low levels of endogenous estradiol and, as a consequence of the latter, they need estrogen hormone replacement therapy (HT). In men, hypoandrogenism has been shown to be associated with subclinical hypothyroidism (15). Thus, women with PCOS may be protected from hypothyroidism by their hyperandrogenism (12). We tested this hypothesis by studying the frequency of hypothyroidism in four different populations with known high or low androgen levels: women with PCOS, women with Turner syndrome, and a population sample of men and women. The findings in the four groups were compared and the aim was to verify or reject the results by studying the prevalence of hypothyroidism in a large population register, representing the total female population from the same region.

## Material and methods

Originally, the women in the PCOS group were diagnosed in 1987 according to a previous histopathological diagnosis of Stein–Leventhal syndrome at wedge resection up to 31 years before the baseline study (16). The ovarian tissue of these women ( $n = 49$ ) was re-examined by an expert pathologist to make sure that the diagnosis of Stein–Leventhal was correct, which it was in 38 cases. These 38 women were invited to the baseline study in 1987 by one of the authors (E.D.). At that time, three of the 38 women were diseased, two declined to participate and three did not want to undergo the physical examinations. Thirty of the women (age 40–59 years) underwent a physical examination, blood sampling and a structured interview of medical history based on a previously validated questionnaire (17,18). In this way, the presence of clinical and/or biochemical hyperandrogenism and oligo- and/or anovulation was ascertained. At follow up in 2008, 32 of the original 38 women were alive and were invited

to a follow-up study (12,19). The data for all the women who were included in the study in 1987 were reevaluated. The Rotterdam criteria were found to be met, based on premenopausal data, but the histopathological diagnosis was converted, based on the established association between the PCO histology and the ultrasound diagnosis (20,21). All of these women, except one, who was excluded, met the Rotterdam criteria (22), as previously described (12,19,23). Twenty-five (78%) of the women (age 61–79 years) underwent blood sampling and a physical examination, and were interviewed using the same structured interview as in 1987 (by J.S. and E.D.). In 2008, all the women were postmenopausal, but only one woman used hormone therapy (HT; 1 mg estradiol, orally).

Since 1995, Turner women  $\geq 18$  years who have attended the Endocrine and the Gynecology out-patient clinics at Sahlgrenska University Hospital, Gothenburg, have been examined by the co-authors, a gynecologist (I.B.) and an endocrinologist (K.L.W.); at Skåne University Hospital, they have been examined by an endocrinologist (K.B.), according to national and international guidelines (24). The women were referred from the pediatric clinic, from gynecologists in the region or from the Turner patient society. The women are examined annually for HT prescription and thyroid blood samples. From 1995, 230 women with Turner syndrome (age 18–78 years) were examined and included in this study; at follow up in 2008, 217 Turner women (age 29–75 years) had been consecutively included. HT was used by 98% of these women at follow up.

A random population sample of 2400 women and men ( $n = 1616$ ), aged 25–64, from the Gothenburg area, was studied in 1995. This was the third population screening by the World Health Organization (WHO), MONItoring of trends and determinants for CARdiovascular disease (MONICA), Gothenburg, Sweden (18). In 1995, hormones were analyzed in every 4th woman in the age groups 25–34 and 35–44, and in all women in the age groups 45–54 and 55–64 ( $n = 662$  in total). At follow up in 2008, 608 of the 662 individuals were traced and

### Key Message

Hypothyroidism during life was less common in hyperandrogenic women with polycystic ovary syndrome, and in men, compared with women in general and women with Turner syndrome, irrespective of age, thyroid peroxidase antibody levels and karyotype. Androgenic hormones seem to protect against hypothyroidism.

invited for a re-evaluation (mean follow-up time 13 years), and were examined by one of two endocrinologists (P.T. and K.L.W.). In total, 95 men and 315 women, aged 38–78 years, participated. One woman in the youngest age group was postmenopausal in 2008 and six women in the two oldest age groups were still menstruating in 2008. HT was used by 31% in 1995 and by 5% of the women at follow up.

All the women >25 years of age in the western region (Region Västra Götaland) of Sweden ( $n = 553\ 716$ ), and all the women in the same region with a PCOS diagnosis ( $n = 3031$ , age 25–87 years) [according to the International Classification of Diseases (ICD), version 10] were identified via the National Board of Health and Welfare Register by the coauthor L.W. In the same register, all women with hypothyroidism (according to ICD 10), with or without PCOS, were identified.

Hypothyroidism was defined as thyroid-stimulating hormone (TSH)  $\geq 4.5$  mU/L and/or by the use of levothyroxine. Thyroid peroxidase antibodies (TPO) were considered positive if levels were  $>60$  kU/L, as defined by the reference value by the laboratory used. Free androgen index (FAI) was calculated as total testosterone divided by serum- (S-) sexual hormone-binding globulin (SHBG)  $\times 100$ . In this study, menopausal age was defined as age  $>50$  years, or an S-FSH  $>50$  U/L (defined by the laboratory used) in WHO MONICA 2008 (17). Smokers were defined as current or never smokers. Hyperandrogenic phenotype was defined as a woman with PCOS presenting with biochemical and/or clinical hyperandrogenism (19). Biochemical hyperandrogenism was defined as total testosterone  $>3.16$  nmol/L and/or androstenedione  $> 6.50$  nmol/L and/or dehydroepiandrosterone sulfate (DHEAS)  $>7.20$   $\mu$ mol/L, and clinical hyperandrogenism as hirsutism, as previously described (12).

A standardized questionnaire, used in other WHO population studies (17,18), was used in all the study populations of the present study (except for the women found in registers in the western region of Sweden), to obtain information on medical history, including information on smoking, medical history and medication.

Fasting venous blood samples were taken between 07:00 h and 10:00 h (in menstruating women on cycle days 5–9 and independent of cycle day in postmenopausal women). The samples were stored at  $-70^{\circ}\text{C}$  and analyzed within 1 year by the Laboratory for Clinical Chemistry, Sahlgrenska University Hospital, which is accredited according to SWEDAC ISO 15189. Total coefficients of variation, including both the intra-assay and the inter-assay variations, are given below. Importantly, similar analysis methods were used in all study groups. Immunofluorescence was used for quantitative determination of

autoantibodies against TPO (Brahms AG, Henningsdorf, Germany), with a detection limit of 0.01 kU/L and a coefficient of variation below 19%. The reference level of TPO was  $<60$  kU/L (12,14). Electrochemiluminescence immunoassay was used in women with PCOS for serum S-TSH and S-free thyroxine (T4) (Roche Diagnostics GmbH, Mannheim, Germany). The S-TSH assay had a detection limit of 0.0051 mU/L and a coefficient of variation  $<7\%$ , and the S-free T4 assay had a detection limit of 0.03 pmol/L and a coefficient of variation  $<10\%$ . S-TSH and S-free T4 were measured with the immunometric method with luminometry (Johnson & Johnson, La Jolla, CA, USA) in women with Turner syndrome and in the WHO MONICA population. The S-TSH (0.2–4.5 mU/L) and S-free T4 (11–22 pmol/L) (14) levels have been described previously. The data were corrected for the relevant reference interval where changes had been made during the follow-up period (14). RIA was used for estradiol and total testosterone in women with PCOS, women with Turner syndrome, and in the women and men in the WHO MONICA 2008 population. For estradiol, the same kit (Clinical Assays, Sauggia, Italy) was used in PCOS, Turner syndrome women and WHO MONICA women and men (12,17). The estradiol assay had a detection limit of 0.04 nmol/L with a coefficient of variation below 16%. For total testosterone, kits from Beckman-Coulter (Fullerton, CA, USA) were used in PCOS women (12), with a detection limit of 1.0 nmol/L and a coefficient of variation below 10%. Kits from ICN Biochemicals Inc. (Diagnostic Division, Costa Mesa, CA, USA) were used in Turner syndrome women and in the WHO MONICA 2008 population (17), with a coefficient of variation below 16%. FAI was calculated as total testosterone/SHBG  $\times 100$ . Chemiluminescent microparticle immunoassay (Abbot Park, Barcelona, Spain) was used for SHBG in women with PCOS (12) (detection limit of 0.1 nmol/L with a coefficient of variation below 9%), and immunoradiometric assay (Orion Diagnostica Oy, Espoo, Finland) was used in women with Turner syndrome and in men and women of the WHO MONICA 2008 population (17), coefficient of variation below 6.3%.

Means, standard deviations and linear correlations were calculated with conventional methods. The  $\chi^2$  test was used for categorical comparisons; however, when the lowest frequency in any of the cells ( $2 \times 2$  table) was below 10, Fisher's exact probability test was used instead. Correlations were adjusted for age and body mass index and tested using Spearman rank order correlation. A  $p$ -value  $<0.05$  was considered significant. All statistical analyses were performed using PREDICTION APPLICATION Software (version 18.0; SPSS, Chicago, IL, USA), and  $\chi^2$  tests and correlations were performed using STATCALC.

All participants gave their written informed consent. The studies were approved on 8 May 2013 by the Ethics

Committee at the University of Gothenburg (Reference number T377-13) and conducted in accordance with the Declaration of Helsinki.

## Results

Characteristics, anthropometric data and hormones for the different study groups are shown in Table 1. In the PCOS group, 60% (15/25) had a hyperandrogenic phenotype. None of the WHO MONICA women had a hyperandrogenic phenotype or had PCOS in their medical history.

Hypothyroidism, at baseline and at follow up, was found in 4 and 8% (ns), respectively, in women with PCOS, in 1% and 3% (ns) in men, in 25 and 34% in women with Turner syndrome ( $p = 0.03$ ), and in 8 and 14% in women from the WHO MONICA population ( $p = 0.01$ ) (Figure 1). The number of women with hypothyroidism was similar in women with and without HT in the WHO MONICA population.

Hypothyroidism >50 years of age was found in 8% of women with PCOS, 4% of men (PCOS vs. men; ns), 43% of women with Turner syndrome ( $p < 0.001$  vs. PCOS), and in 17% of the women in the WHO MONICA population ( $p < 0.01$  vs. PCOS) (Table 1). Hypothyroidism increased with age in women with Turner syndrome and in women from the WHO MONICA population, in contrast to women with PCOS and men (Figure 1).

At follow up, TPO levels were elevated in 20% of the women with PCOS. At start and follow up, TPO was elevated in 3 and 5% of men, respectively (ns). In women with Turner syndrome, the corresponding figures were 36 and 37% (ns), and in women in the WHO MONICA study, in 18 and 18% (ns) (Figure 2). Elevated TPO levels were higher in women with Turner syndrome than in men and women in the WHO MONICA population (both  $p < 0.0001$ ) and in women with PCOS ( $p = 0.05$ ) (Figure 2). Elevated TPO levels did not change with aging in any of the women.

Among individuals >50 years of age, 20% of PCOS women, 50% of Turner women, 7% of men and 21% of women in the WHO MONICA population had elevated TPO levels (Table 1). TPO did not differ between women with PCOS and men (ns), or in women with PCOS and women in the WHO MONICA study (ns). Elevated TPO antibodies were more common in Turner women than in WHO MONICA women ( $p = 0.0001$ ), in Turner women than in men ( $p < 0.0001$ ) or PCOS women ( $p = 0.05$ ), and in WHO MONICA women than in men ( $p < 0.02$ ) at follow up.

The highest levels of serum estradiol were found in premenopausal women in the WHO MONICA study and

in women with Turner syndrome (most of them on HT) (Table 1).

The levels of serum total testosterone were highest in men, followed by the levels in women with PCOS, thereafter by levels in women in the WHO MONICA population. The lowest levels were found in women with Turner syndrome (Table 1).

Hypothyroidism was evenly distributed in the different karyotypes of women with Turner syndrome. Hypothyroidism was found in 29% of women with 45X, in 26% of women with true mosaicism due to 45X/46XX, in 17% with an iso-chromosome, in 25% of women with a ring chromosome and in 23% of women with a Y chromosome.

In the total female population, 6.8% (37 475/553 716) had a diagnosis of hypothyroidism. In this register study, 5.5% (168/3031) of the women with PCOS also had a diagnosis of hypothyroidism ( $p = 0.007$ ).

S-testosterone and FAI declined and S-TSH increased with age in all the groups studied. After adjustment for age and body mass index, there were no significant correlations in any group between S-total testosterone or FAI and S-TSH, either at the start of the study or at follow up. There were no correlations between FAI and S-TSH in any of the study groups, with or without positive TPO, after adjustment for body weight.

## Discussion

Hypothyroidism was less common during follow up in women with PCOS with persistent hyperandrogenism after the menopause, and in men, compared with women in general and with women with Turner syndrome. This was not explained by autoimmunity or the Y-chromosome. Thus, androgens seem to protect against hypothyroidism. Furthermore, our previous incidental finding of a lower frequency of hypothyroidism in women with PCOS (12) was confirmed in a large population cohort of more than 550 000 women from the same region.

Hypothyroidism is often caused by autoimmunity (25) and TPO is used as an indicator of this. However, in the present study, elevated TPO levels were similar in women with PCOS and in women in the WHO MONICA population. Despite this finding, women with PCOS did not develop hypothyroidism to the same extent as did women without PCOS. Thus, autoimmunity does not seem to be the reason for the difference in hypothyroidism frequency in these two groups. However, TPO levels within the reference range do not preclude hypothyroidism.

In women with Turner syndrome and ongoing HT, high proportions of elevated TPO (50%) and hypothyroidism (43%) at ages >50 years were found. Additionally, women with Turner syndrome had the lowest levels of testosterone compared with all the other groups. This

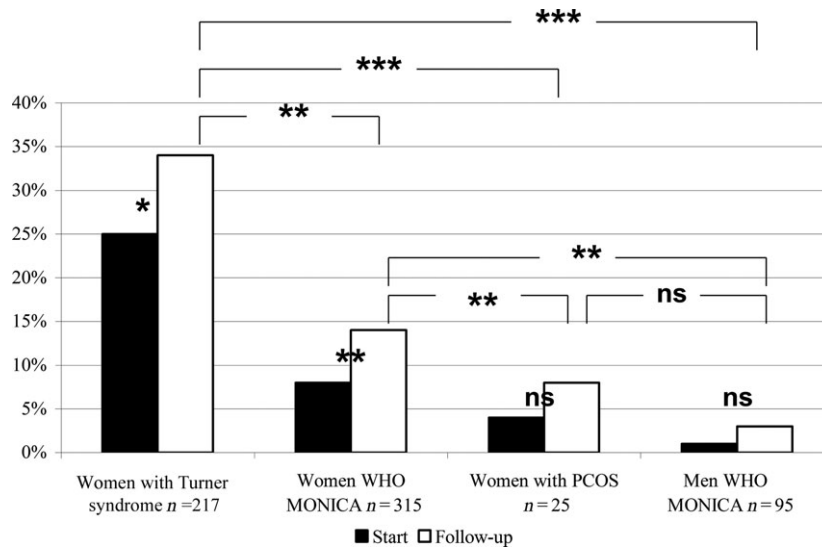


**Table 1.** Characteristics, hormone levels, prevalence of hypothyroidism including levothyroxine and estrogen hormone replacement therapy (HT) in the population sample (WHO MONICA study), in women with polycystic ovary syndrome (PCOS) and in women with Turner syndrome (TS) in 2008. Means and standard deviations (SD) are presented. The total number of participants in the respective groups is given. The respective groups are divided into groups based on age: ≤50 and >50 years. The menopausal age in this study was defined as age >50 years, or as verified by serum follicle-stimulating hormone (FSH) >50 U/L, as defined by the laboratory used.

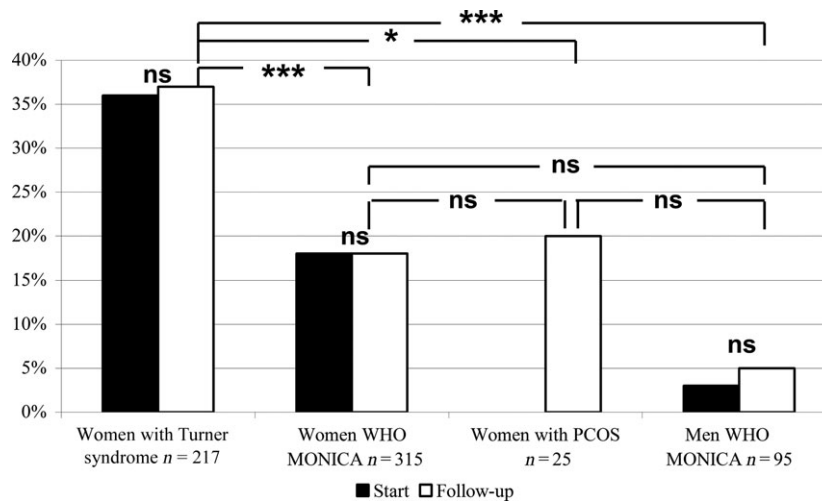
	Women WHO MONICA						Men WHO MONICA						Women with PCOS						Women with TS					
	≤50 years			>50 years			≤50 years			>50 years			≤50 years			>50 years			≤50 years			>50 years		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Age (years)	315	63.7	8.9	69	43.9	2.7	246	67.6	5.2	40	44.3	3.0	55	66.2	6.3	25	70.4	5.0	217	29.4	11.9	188	27.1	8.3
BMI(kg/m <sup>2</sup> )	26.6	5.0	25.4	4.8	26.9	5.3	27.1	3.4	26.2	4.0	27.5	3.1	27.1	5.0	24.8	4.5	24.8	4.6	24.8	4.6	24.6	4.3	24.8	4.6
WHR	0.84	0.07	0.83	0.07	0.84	0.08	0.84	0.08	0.86	0.12	0.96	0.07	0.85	0.10	0.82	0.07	0.81	0.07	0.82	0.07	0.81	0.07	0.86	0.09
Smoking (%)	9		4		10		14		10		16		12		1		1		1		1		1	
TSH (mIU/L)	2.42	1.33	2.15	1.21	2.65	1.67	2.35	1.14	2.01	1.05	2.53	1.23	2.05	1.02	3.47	1.28	3.54	1.35	3.47	1.28	3.54	1.35	2.66	3.70
Free T4 (pmol/L)	16.1	1.1	16.1	2.1	16.2	3.1	16.5	1.1	16.3	2.1	16.6	1.9	17.44	3.417	14.9	4.2	14.5	3.2	14.9	4.2	14.5	3.2	18.3	3.6
Estradiol (nmol/L)	0.087	0.218	0.280	0.225	0.050	0.184	0.079	0.022	0.078	0.021	0.080	0.026	0.040	0.006	0.153	0.291	0.187	0.204	0.153	0.291	0.187	0.204	0.068	0.079
Testosterone (nmol/L)	1.18	0.31	1.18	0.28	1.17	0.33	1.455	4.20	17.70	3.10	13.20	4.80	1.41	0.45	0.94	0.63	0.94	0.52	0.94	0.63	0.94	0.52	0.64	0.31
SHBG (nmol/L)	70.1	29.3	56.6	19.2	77.2	34.5	49.8	19.1	46.6	18.5	52.5	19.8	56.1	23.0	49.3	39.7	49.2	44.2	49.3	39.7	49.2	44.2	44.4	24.7
FAI	1.68	1.03	2.08	1.58	1.52	0.96	29.4	21.9	38.0	16.8	1.51	0.96	2.87	1.44	1.91	1.59	1.91	1.14	1.91	1.59	1.91	1.14	1.44	1.25
Anti-TPO positive (%)	18.4		10.0		20.7		5.3		2.5		7.3		20.0		36.9		32.9		36.9		32.9		50.0	
Hypothyroidism (%)	13.6		2.9		17.0		3.2		2.5		3.6		8.0		34.0		25.0		34.0		25.0		41.8	
Levothyroxine <sup>a</sup> (%)	10.5		1.4		13.0		3.2		2.5		3.6		8.0		31.3		21.8		31.3		21.8		41.4	
HT treatment (%)	5		4		5		0		0		0		0		98		99		98		99		97	

N, number studied; Total, total number of participants in the respective groups; BMI, body mass index; WHR, waist/hip ratio; TSH, thyroid -stimulating hormone; T4, thyroxine; Testosterone, total testosterone; SHBG, sexual hormone-binding globulin; FAI, free androgen index (total testosterone/SHBG × 100); TPO, thyroid peroxidase antibodies; HT, estrogen hormone replacement therapy. The conversion factors are as follows: divide estradiol by 0.00367 for picograms per milliliter, SHBG by 34.67 for micrograms per deciliter and testosterone by 0.0347 for nanograms per deciliter.

<sup>a</sup>Levothyroxine supplementation in women and men with hypothyroidism, respectively.



**Figure 1.** Prevalence of hypothyroidism (%) in women and men among the populations at the respective starts of the studies and at follow up in 2008: Turner women, women from the WHO MONICA population, women with PCOS and men from the WHO MONICA population. Hypothyroidism was defined as thyroid-stimulating hormone  $\geq 4.5$  m IU/L and/or by use of levothyroxine. The total number of participants (n) in the respective groups in 2008 is given. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , ns = not significant.



**Figure 2.** Prevalence of thyroid peroxidase (TPO)-positive (%) women and men among the populations at the respective starts of the studies and at follow up in 2008: Turner women, women from the WHO MONICA population, women with PCOS and men from the WHO MONICA population. The total number of participants (n) in the respective groups in 2008 is given. In women with PCOS, TPO antibodies were not obtained at baseline. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , ns = not significant.

might suggest that hyperandrogenism is associated with a lower risk of hypothyroidism. This is supported by the present finding that women with PCOS do not differ from men regarding the frequency of hypothyroidism. Women with PCOS are known to remain hyperandrogenic after the menopause (12). The Y-chromosome in men could be the reason for the difference in hypothyroidism prevalence between men and women; however,

this was contradicted by the fact that women with Turner syndrome who harbored a Y-fragment had a similar proportion of hypothyroidism (23%) as did women with other Turner karyotypes (~25%) (26). The interplay between the sex chromosome (X or Y), sex hormones and hypothyroidism has been studied in animals without any firm conclusion regarding causality for the development of thyroid disease (27).

Hypothyroidism increases with increasing age (28,29) and this association was also found in non-hyperandrogenic groups in this study. The cut-off of >50 years was of importance to be able to study an exclusively postmenopausal group. Besides, age adjustment was also performed in the correlation analyses. The TPO levels were fairly stable throughout life. Hypothyroidism in postmenopausal women in the present study was unaffected by the use of HT.

The limitations of this study were that the number of women from which our hypothesis originated was fairly small, as were the number of women aged >50 years in some of the groups studied. Another limitation was that no data on androgens, S-TSH, S-free T4 or TPO were available in the women with PCOS in the large population register study. Further, liquid chromatography mass spectrometry would have been preferable for the hormone analysis. However, that method was not available in the laboratory at the time of the investigation. Furthermore, correlations between androgens and TSH, free T4 and free T3, respectively, were difficult to assess, due to the influence of levothyroxine treatment.

A strength of this study was that thyroid hormones were analyzed using similar methods at the accredited laboratory of the same hospital in all study groups in 2008. Moreover, all groups were followed for a long period of time, 10–21 years, and the data on the use of levothyroxine were reliable. In addition, a random population sample is considered to be the best control group. Data regarding PCOS and hypothyroidism were also validated in a large sample via registers from the same region using ICD 10 diagnoses.

In conclusion, hypothyroidism was less frequent in women with PCOS and in men, compared with women in the general population and with women with Turner syndrome. This could not be explained by altered autoimmunity or the Y-chromosome. Thus, androgens seem to protect against hypothyroidism.

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