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Prevalence of Thyroid Disorders in the Working Population of Germany: Ultrasonography Screening in 96,278 Unselected Employees

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Germany continues to be iodine deficient despite considerable improvement in the past years. To assess the current prevalence of diffuse and/or nodular thyroid disorders, a cross-sectional observational study in a nonrandom sample of the working population was carried out throughout Germany in 2001 and 2002. A total of 96,278 employees 18–65 years of age from 214 companies or other private or public institutions voluntarily underwent ultrasonographic examinations by 230 experienced investigators. To compare the prevalence of different abnormal findings in relation to age and gender, descriptive statistics and the Kruskal-Wallis test were used. Data from volunteers with previous thyroid treatment (13.0% of total sample) were not included in the analysis. Abnormal findings (goiter and/or nodules $>$ 0.5 cm) were observed in 33.1% (men, 32.0%; women, 34.2%) of the examined patient population, an enlarged thyroid without nodules in 9.7% (men, 11.9%; women, 7.6%), nodules only without enlargement of the thyroid in 14.3% (men, 11.5%; women, 17.0%), and nodular goiter in 9.1% (men, 8.6%; women, 9.6%). Nodules (with or without goiter) between 0.5 and up to 1.0 cm were found in 10.0%, and nodules above 1.0 cm in 11.9% of the population. Rates of abnormal findings increased with age in both genders. Goiter was more common in men, nodules in women. In light of these findings, the prevalence of thyroid disorders in Germany continues to be high. Although the study may slightly overestimate the prevalence, about one third of the working population is affected and remains unaware of this condition. These results emphasize the importance of effective sonographic screening to detect early thyroid abnomalities in order to initiate preventive and therapeutic measures to prevent the onset or progression of disease and its sequels.

Introduction

The 1998 World Health Organization (WHO) survey classified Germany as an area of iodine deficiency and stated that there were nonlegislative efforts to improve the present status of iodine intake. Although recent reports show that there is an ongoing, albeit slow, improvement of iodine intake in Germany (1–4), the WHO recommendation of a minimum intake of 150 to 300 μg of iodine per day has not been achieved. Iodine deficiency is the main cause for the development of goiter, which prior surveys showed to occur at a prevalence of 20%–30% in the general population (5,6).

To assess the present situation in Germany, several institutions joined together to conduct a large-scale screening, named Papillon, focusing on the detection of previously unknown thyroid disorders. The aims of the initiative were to reveal by ultrasound frequency and type of morphologic thyroid abnormalities among the working population in Germany. The intention was to assess the prevalence of diffuse and nodular goiter in the German population and to increase public awareness concerning thyroid disorders. As occupational prevention is widely practiced in German companies, occupational physicians were important partners in this screening effort. It is also easier in an industrial setting to gain access to large numbers of "healthy" workers as well

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TABLE 1. CHARACTERISTICS OF SCREENED VOLUNTEERS (n = 96,278)

	Women	*Men*	*Total*
Gender (%)	53.9	46.1	100
Age (years)[a]	40.4 ± 10.8	42.5 ± 10.3	41.4 ± 10.6
Height (cm)[a]	166.4 ± 6.5	179.1 ± 7.2	172.2 ± 9.3
Weight (kg)[a]	67.2 ± 13.0	83.3 ± 12.8	74.5 ± 15.2
Body mass index (kg/m^2)[a]	24.3 ± 4.7	26.0 ± 4.2	25.1 ± 4.6
Previous thyroid treatment	18.1	7.1	13.0
Drug treatment (%)	16.6	6.3	11.9
Surgery (%)	3.4	1.3	2.4
Radioiodine therapy (%)	0.7	0.3	0.5

[a]Values are shown as mean ± standard deviations.

as to initiate health programs for early prevention of chronic diseases (7).

Methods

Participants

In a variety of different companies throughout Germany as well as in private, academic, or public institutions, employees 18–65 years of age were informed about the possibility of participating in the thyroid screening program. There were no exclusion criteria limiting participation.[a] Thus, a voluntary nonrandom sample of employees underwent the examinations.

Investigations

The participants were questioned about whether they were aware of any preexisting thyroid disease and whether they had had any thyroid-specific pretreatment. The volunteers were examined by experienced investigators (a total of 230 specialists in internal medicine, endocrinology, nuclear medicine, or occupational medicine). A standardized questionnaire served for documentation. The first part was answered by the volunteers asking for information about previous thyroid treatment. The second part was filled in by the sonographer for documentation of the ultrasound findings. The volunteers were informed about the results of ultrasound screening by handing out a copy of the standardized documentation form. In case of abnormal findings, they were asked to visit an expert for further diagnostics.

Ultrasonography and volumetry of thyroid glands and thyroid nodules

All investigations were performed using high-resolution ultrasonography (Sonoline ADARA LC with 7.5 MHz; Siemens, Germany). Volumes of thyroid glands and nodules were calculated according to the ellipsoid model (length [cm] × width [cm] × depth [cm] × 0.5) (8,9). In a subgroup of 10 volunteers, 10 sonographers from one institution (Würzburg) determined accuracy as well as intraobserver and interobserver variability of the ellipsoid method in comparison to volume determinations by three-dimensional-ultrasound as the gold standard. The ellipsoid method systematically overestimated the "real" thyroid volume by 17%. The mean intraobserver variability amounted to 17.1% and the mean interobserver variability to 17.9% (16).

Ultrasound findings were classified by the examiner into four major categories: (1) no goiter and no nodules (goiter was defined as a thyroid volume > 25 mL in men and 18 mL in women), (2) enlarged thyroid without nodules, (3) nodules only (focal lesions > 0.5 cm) without goiter, and (4) nodular goiter. In addition, the size of the nodules was categorized as either between 0.5 and 1.0 cm, or greater than 1.0 cm.

Statistical analysis

For comparison of prevalence, odds ratios were calculated and tested using the likelihood ratio χ^2. Distributions of continuous variables were displayed using box-plots and summarized by mean values and standard deviations. Semilogarithmic plots and geometric means were calculated for thyroid volumes because of the skewness of the underlying distributions of the data.

Results

Study settings

Two hundred fourteen different companies or institutions participated in the initiative between January 2001 and December 2002 (see Appendix). Between 21 and 3,463 volunteers (median, 289) were screened at each site.

Sample description

Table 1 displays the background characteristics of the individuals screened. Of the 96,278 volunteers, 20.0% were living in the north, 39.0% in the west, 15.2% in the east, and 25.8% in the south of Germany. The sample was well balanced for gender: women, 53.9%; and men, 46.1%. According to the questionnaires, the vast majority of participants did not have any previous thyroid treatment (n = 83,757; 87.0%), and only these 83,757 subjects without pretreatment were included in the statistical evaluation.

Findings by region

Abnormal findings (i.e., goiter and/or nodules) were reported in 33.1% of volunteers: 30.5% in the west (Nordrhein-

[a]A list of all participating institutions/companies may be found on pg. 930.

Westfalen, Hessen), 32.2% in the north (Schleswig-Holstein, Hamburg, Bremen, Niedersachsen), 34.7% in the south (Rheinland-Pfalz, Saarland, Baden-Württemberg, Bayern), and 38.2% in the east (Mecklenburg-Vorpommern, Brandenburg, Berlin, Sachsen-Anhalt, Sachsen, Thüringen). Nodular disease was found in 9.1%: 7.4% west, 8.7% north, 10.5% south, 11.4% east. Overall goiter prevalence was 9.7%. The odds ratio for having thyroid disorders in the north compared to the south was 0.95 (0.90–0.996). Mean thyroid volume was 17.1 mL (standard deviation [SD]: 9.9 mL): 16.7 mL in the west, 17.8 mL in the north, 17.5 mL in the south, and 16.5 mL in the east.

Findings according to gender and age

Thyroid volumes according to gender and age groups are displayed in Figure 1. In all age groups, thyroid volumes were significantly higher in men than in women. In older individuals, higher rates of abnormal findings (enlarged thyroid and/or nodules) were noted in both genders. However, mean thyroid volumes peaked at 45 years of age and showed no further increase in higher age groups.

The horizontal lines (18 mL for women, 25 ml for men) indicate the limits for the definition of goiter (Fig. 1). The prevalence for the different categories of abnormal findings is given in Table 2. Goiter prevalence (with or without nodules) increased from the youngest to the oldest age group from 4.5% to 25.1% in women and from 3.5% to 27.7% in men. Nodular goiter prevalence in particular increased from the youngest to the oldest age group from 1.2% to 18.0% in women and from 0.5% to 14.5% in men.

Figure 2 shows nodule prevalence (with or without goiter) according to gender and age. While thyroid volumes and the prevalence of goiter without nodules were lower in women than men, nodules were more frequent in all age groups. Also, in both genders, nodule prevalence increased steadily from the youngest to the oldest age group, without any limit or "plateau" effect.

In summary, the prevalence of abnormal thyroid findings in untreated subjects increased with age from 12.1% to 51.9% in women and from 8.0% to 45.2% in men.

Discussion

The present large-scale screening study demonstrated three main findings. First, abnormal thyroid findings, revealed by ultrasonographic examinations, were identified in approximately 33% of all individuals screened. Second, the prevalence of thyroid disorders increased with age, although approximately 10% of individuals < 25 years of age were also affected. Third, in contrast to previous reports, men and women were affected to a similar extent.

The study group investigated a large sample of the general population. According to strict statistical criteria, the study may overestimate the prevalence of thyroid abnormalities because the sample was not drawn by random and the volunteers "referred" themselves. The only selection criteria, however, was the willingness of the individuals to participate in the study. Examinations at the workplace provided access to healthy individuals who do not regularly see their primary care physician, or would not be willing to participate in offsite examinations.

The study group did not generally apply any invasive investigations such as laboratory tests, because this would potentially have reduced the participation in the survey. In a subgroup of 572 volunteers from one site (Würzburg), iodine excretion of a spot urine sample, serum thyrotropin (TSH), free thyroxine (FT_4), and free triiodothyronine (FT_3) has been determined. In 462 of those volunteers without any previous thyroid treatment, the mean urinary iodine excretion was 116.1 μg/L. According to WHO criteria, iodine deficiency grade I was prevalent in 32.5%, grade II in 17.9%,

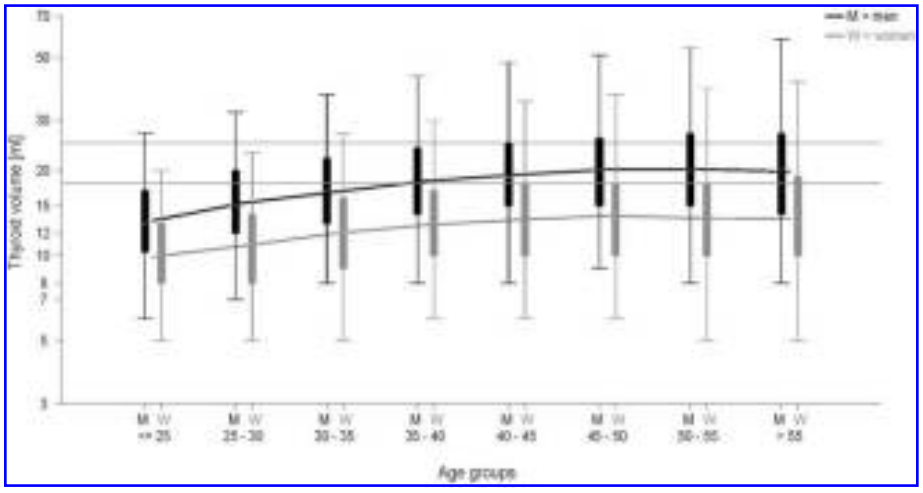

FIG. 1. Thyroid volume by gender and age group. For each age group, separate box-and-whisker plots for men (black) and women (gray) are presented. The boxes cover the middle 50% of thyroid volumes of the corresponding sample; i.e. the lower (upper) bounds of the boxes mark the first (third) quartiles. The whiskers cover the middle 95% of thyroid volumes of the corresponding sample; i.e. the lower (upper) bounds of the boxes mark the 2.5% (97.5) quantiles. The polygons connect the geometric means for each age group according to gender. Horizontal lines indicate limits for the definition of goiter (men: > 25 mL, women: > 18 mL).

TABLE 2. PREVALENCES OF THYROID DISORDERS/ODDS RATIOS IN COMPARISON TO YOUNGEST GROUP/ ODDS RATIOS IN COMPARISON TO FEMALE GENDER IN THE WORKING POPULATION AT ULTRASONOGRAPHIC SCREENING (ONLY FOR MEN), BY GENDER AND AGE GROUP

	No abnormal findings %	*Abnormal findings (goiter and/or nodules) %/odds ratio*[b,c]	*Enlarged thyroid without nodules %/odds ratio*[b,c]	*Nodules only (0.5 cm)*[a] *%/odds ratio*[b,c]	*Nodular goiter %/odds ratio*[b,c]
Women untreated	65.5	34.2	7.6	17.0	9.5
Up to 25 yrs	87.6	12.1/1.0	3.3/1.0	7.6/1.0	1.2/1.0
26–30 yrs	81.8	17.8/**1.6**	4.6/**1.4**	10.5/**1.4**	2.7/**2.3**
31–35 yrs	73.4	26.3/**2.6**	8.0/**2.6**	12.6/**1.8**	5.6/**4.8**
36–40 yrs	65.3	34.4/**3.8**	9.0/**2.9**	16.7/**2.4**	8.7/**7.7**
40–45 yrs	59.4	40.3/**4.9**	9.4/**3.0**	19.0/**2.8**	11.9/**11.0**
45–50 yrs	54.9	44.8/**5.9**	9.5/**3.1**	21.2/**3.3**	14.1/**13.3**
50–55 yrs	51.5	48.2/**6.8**	7.6/**2.4**	24.5/**3.9**	16.2/**15.6**
Over 55 yrs	47.6	51.9/**7.8**	7.1/**2.3**	26.9/**4.5**	18.0/**17.7**
Men untreated	67.7	32.0	11.9	11.5	8.6
Up to 25 yrs	91.7	8.0/1.0/**0.6**	3.0/1.0/0.9	4.5/1.0/**0.6**	0.5/1.0/**0.4**
26–30 yrs	83.6	16.2/**2.2**/0.9	7.2/**2.5**/**1.6**	6.9/**1.6**/**0.6**	2.0/**4.1**/0.7
31–35 yrs	78.0	21.7/**3.2**/**0.8**	9.5/**3.4**/**1.2**	8.4/**1.9**/**0.6**	3.8/**7.7**/**0.7**
36–40 yrs	71.5	28.2/**4.5**/**0.8**	11.9/**4.4**/**1.4**	9.6/**2.2**/**0.5**	6.7/**14.2**/**0.8**
40–45 yrs	65.0	34.7/**6.1**/**0.8**	13.5/**5.1**/**1.5**	11.9/**2.8**/**0.6**	9.3/**20.1**/**0.8**
45–50 yrs	58.9	40.8/**7.9**/0.9	15.0/**5.8**/1.7	13.5/**3.3**/**0.6**	12.4/**27.8**/**0.9**
50–55 yrs	56.3	43.3/**8.8**/**0.8**	14.4/**5.5**/**2.1**	15.2/**3.8**/**0.6**	13.7/**31.2**/**0.8**
Over 55 yrs	54.6	45.2/**9.5**/**0.8**	13.2/**4.9**/**2.0**	17.5/**4.5**/**0.6**	14.5/**33.5**/**0.8**

(n = 83,757 employees, bold figures: odds ratio significantly different from 1, $p < 0.05$.
[a]Thyroid not enlarged.
[b]Odds ratio in comparison to youngest group.
[c]Odds ratio in comparison to female gender.

and grade III in 5.2%. The serum measurements of TSH and free thyroid hormones revealed latent hyperthyroidism (TSH suppressed FT_3 and/or FT_4 normal) in 4.5% and manifest hyperthyroidism (TSH suppressed, FT_3 and/or FT_4 elevated) in 0.4%. Accordingly, latent hypothyroidism (TSH increased FT_3 and/or FT_4 normal) was detected in 2.3% of the volunteers whereas no single case of manifest hypothyroidism (FT_3 and/or FT_4 decreased) was observed. Elevated autoantibodies against thyroid peroxidase (TPO) and thyroglobulin (TG) were detected in 13.3% and 10.5%, respectively.

The use of high-resolution ultrasound is generally considered the first choice for the evaluation of thyroid size and morphology (10–13). It is much more reliable than palpation of the gland, which has an accuracy of only approximately 40% (14) and reduces the interobserver variation which is unavoidable in a multi-center survey like this. In comparison to the two-dimensional rotational ellipsoid method used

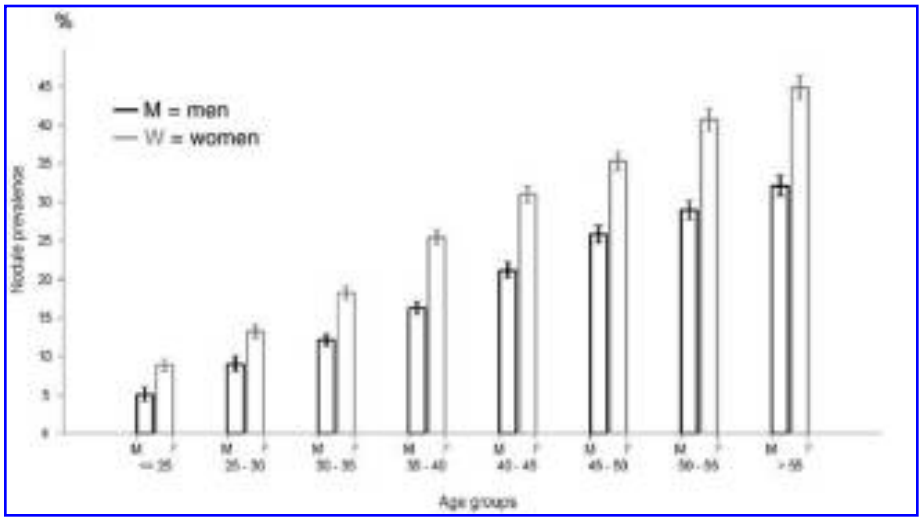

FIG. 2. Nodule prevalences by gender and age group. The column heights represent observed prevalences. The column tops are surrounded by 95% confidence limits for true prevalences.

for volumetry, three-dimensional procedures would have been more accurate (15,16). However, computed tomography (CT), magnetic resonance imaging (MRT), or three-dimensional ultrasound are not applicable for large scale screening in a sample of approximately 100,000 volunteers because of radiation exposure, costs, and/or time needed. Moreover, there is an ongoing debate on the need for population-specific thyroid volume references and the definition of goiter (15). In this study, in order to keep such variation to a minimum, goiter diagnosis was not left to the clinical judgement of the respective examiner, but was derived from quantitative measurements.

Surveys on thyroid disorders are difficult to compare because the selection, size, and composition of samples, methods, settings, and outcomes vary substantially. However, the available German data are consistent in their high prevalences of goiter and thyroid structure abnormalities (16–18). Ultrasonographic examinations have been found useful in the detection of small, nonpalpable thyroid nodules (thyroid incidentalomas) in several prospective studies, with prevalence rates of 17% in Brazil (19), 19% in Belgium (20), 27% in Finland (21), and 67% in the United States (22).

The prevalence of thyroid disorders is still surprisingly high. Germany is a country with long-standing moderate iodine deficiency. Apparently the iodine intake of the German population has improved over the last decades (1,2), because of by increased use of iodized table salt and salt for industrial food production. However, the situation is still not satisfactory (4), and Germany failed to eliminate iodine deficiency by the year 2000, as had been stipulated by the Rome Conference on Nutrition of the WHO in 1990 (23). Recent data indicate that German iodine intake amounts to only 70% of that recommended by the WHO (4). Most of the adults in the sample had been exposed to iodine deficiency in their childhood and adolescence, and the improved iodine intake in Germany is likely to have had only a limited effect on this group. This is consistent with the increased prevalence of thyroid disorders with increasing age. It may take many years before a major change in iodine intake is followed by a positive influence on the occurrence of thyroid disease (24).

Consequently, the efforts to optimize the iodine supply have to be maintained in Germany. Such efforts will be of particular benefit for the younger population. Prophylaxis without ascertaining its effectiveness, however, is not sufficient in light of the high prevalence of thyroid disease. In addition to prophylaxis, screening of the adult population for thyroid disorders is necessary. Particular attention should be paid to the screening of men, because of the higher prevalence of goiter in men compared to women. Men also have a substantial prevalence of nodules, even if not as high as in women.

How should goiter and thyroid nodules be dealt with after having been detected during screening? Although the treatment of diffuse goiter with thyroid hormones in individually adjusted dosages (and supplemental iodine) is standard in this age group there is currently no unequivocal answer to the question of nodule management.

Subjects with nodules should be examined carefully. The vast majority of nonpalpable small nodules are histologically benign and the potential for malignancy is low (25). However, because nonpalpable papillary thyroid cancer is at times associated with local or even distant metastases, thyroid "incidentalomas" have to be taken seriously and careful follow-up is necessary (27,26). According to the guidelines of the German Society of Nuclear Medicine, fine-needle aspiration biopsy should be performed in inactive (cold) nodules greater than 10 mm in diameter (27).

Study participants with thyroid abnormalities (diffuse goiter and/or nodules) were asked by the screening physicians to visit a physician experienced in diagnosis and treatment of thyroid diseases. No systematic follow-up of those examinations has been organized in the framework of the Papillon Initiative. However, the study organizers received notice of 15 cases of thyroid cancer, which have been detected by the screening initiative (28).

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List of All Participating Institutions/Companies

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