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Effects on Bone Mass of Long Term Treatment with Thyroid Hormones: A Meta-Analysis*

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ABSTRACT

Osteoporosis is the main cause of spine and hip fractures. Morbidity, mortality, and costs arising from hip fractures have been well documented. Thyroid hormones (TH) are widely prescribed, mainly in the elderly. Some studies (but not all) found a deleterious effect of suppressive TH therapy on bone mass. These conflicting data raised a controversy as to the safety of current prescribing and follow-up habits, which, in turn, raised major health-care issues. To look for a detrimental effect on bone of TH therapy, we performed a meta-analysis (by pooling standardized differences, using a fixed effect model) of all published controlled cross-sectional studies (41, including about 1250 patients) concerning the impact of TH therapy on bone mineral density (BMD). Studies with women receiving estrogen therapy were excluded *a priori*, as were studies with a high percentage of patients with postoperative hypoparathyroidism, when no separate data were available. We decided to stratify the data according to anatomical site, menopausal status, and suppressive or replacement TH therapy, resulting in 25 meta-analyses on 138 homogeneous subsets of data. The main sources of heterogeneity between studies that we could identify were replacement or suppressive TH therapy, menopausal status, site (lumbar spine, femoral neck, Ward's triangle, greater trochanter, midshaft and distal radius, with various percentages of cortical bone), and history of hyperthyroidism, which has recently been found to impair bone mass in a large epidemiological survey. To improve homogeneity, we excluded *a posteriori* 102 patients from 3 studies, who had a past history of hyperthyroidism and separate BMD data, thus allowing assessment of the TH effect in almost all 25 subset meta-analyses. However, controls were usually not matched with cases for many factors influencing bone mass, such as body weight, age at menarche and at menopause, calcium dietary intake, smoking habits, alcohol intake, exercise, *etc.* For lumbar spine and hip (as for all other sites), suppressive TH therapy was associated with significant bone loss in postmenopausal women (but not in premenopausal women), whereas, conversely, replacement therapy was associated with bone loss in premenopausal women (spine and hip), but not in postmenopausal women. The detrimental effect of TH appeared more marked on cortical bone than on trabecular bone. Only a large long term prospective placebo-controlled trial of TH therapy (*e.g.* in benign nodules) evaluating BMD (and ideally fracture rate) would provide further insight into these issues. (*J Clin Endocrinol Metab* **81:** 4278–4289, 1996)

SINCE VON Recklinghausen's first description of reduced bone mass in untreated thyrotoxicosis in 1891, this condition has been well known to increase bone turnover, acting mainly on bone resorption (resulting in increased urinary excretion of pyridinium cross-links and decreased serum PTH and 1,25-dihydroxyvitamin D_3), but also on osteoblast activity (resulting in elevated osteocalcin and bone alkaline phosphatase) (1, 2). The consequent osteopenia, assessed by bone densitometry (3), affects both cortical and trabecular bone, the former predominantly, a conclusion drawn from histomorphometric studies of endogenous (4, 5) or exogenous hyperthyroidism (6). If prolonged, this situation would lead to osteoporosis and fractures (7). Conventional T_4 therapy is often associated with subclinical hyperthyroidism (*i.e.* low TSH), even when prescribed as replacement therapy (8). Whether subclinical hyperthyroidism resulting from long term exposure to exogenous thyroid hormones (TH) induces bone loss remains debatable. In 1987, Ross *et al.* (9) published the first controlled study that found a statistically significant bone loss. Their report was rapidly followed by others that came to the same alarming conclusion. Conversely, more recent studies using a similar methodology failed to demonstrate any detrimental effect of TH on bone mineral density (BMD), a strong predictor of hip and spine fractures (10–13). The lifetime risk of hip fracture is about 17% for white American women 50 yr of age (14) and 33% for women living to age 90 yr (15). These conflicting data on the bony effects of TH therapy led to a controversy as to the safety of current prescribing habits (15–20) and to recommendations to reduce T_4 doses and to monitor patients more closely (TSH) (21). This advice together with indirect costs arising from spine and hip fractures facilitated by TH-induced bone loss would result in major cost increases, because TH are among the drugs most prescribed to women, at least in the United States (22) and Germany (23), and morbidity, mortality, and expense resulting from hip fractures have been well documented (24). Overtreatment with TH is common; 59% of 1180 Scottish patients receiving T_4 replacement had their TSH suppressed (25). Therefore, this controversy raises major health-care issues. The confirmation of a detrimental effect of subclinical hyperthyroidism due to overtreatment or intentional suppressive therapy would have two major consequences: 1) the need for careful titration of the TH dose and for closer monitoring of serum TSH, as a 25-μg increase in T_4 dose may suppress TSH in patients with previously normal

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TSH levels (26); and 2) the restriction of suppressive therapy to thyroid cancer, as even the short term efficacy of TH in limiting nodule or goiter growth has never been proven by a randomized placebo-controlled trial. Undertreatment with TH is also common, and the resulting subclinical hypothyroidism may be harmful (increased risk of coronary disease from hypercholesterolemia; stimulation of residual tumoral cells after thyroidectomy for cancer).

Studies dealing with the effects of TH on bone were usually cross-sectional and included a small number of patients, with variations in sex ratios, menopausal status, and many baseline characteristics, thus decreasing the chance of finding statistically significant differences from controls and increasing the risk of missing a real difference (type 1 and 2 errors, respectively). No randomized controlled trial of reasonable size and duration has been published. In the first meta-analysis published on this issue, which was restricted to the effect of suppressive therapy, Faber and Galloe (27) concluded that suppressive L-T_4 therapy induced a statistically significant bone loss in postmenopausal women, but not in premenopausal women. However, their meta-analysis omitted a few studies meeting their inclusion criteria and published between 1985 and 1992 (the period set for overview). They did not provide thorough information on their methodology (28) and did not use a continuous variable such as BMD for the meta-analysis, which is the recommended method of Hedges and Olkin (29) as modified by Whitehead and Whitehead (30). Moreover, since 1992, many other cross-sectional studies have been published. Therefore, we decided to pursue our meta-analysis, hoping that it would allow firmer conclusions and better identification of the subgroups of patients and anatomical sites more prone to bone loss. Our meta-analysis set out to explore several issues. Does effective TH-suppressive therapy have a detrimental effect on BMD? Do exogenous TH (regardless of whether they suppress TSH) have a detrimental effect on bone mass when combining all available studies? Does suppressive therapy induce greater bone loss than replacement therapy (dose-effect relationship)? Are postmenopausal women more prone to TH-induced bone loss? Which site displays the most severe bone loss? Finally, does the detrimental effect of TH correlate with the proportions of cortical and cancellous bone at the various sites?

Materials and Methods

Papers or abstracts published between January 1982 and December 1994 were searched for in Medline and Current Contents under the following headings: thyroid hormones, L-T_4, and bone density. We also looked at the annual tables of contents of the most referenced periodicals and screened references from the relevant literature, including reviews and editorials. We were careful to avoid duplication. When additional data were needed, the authors were asked to provide them. Finally, the companies marketing TH in France (Merck and Roche) were asked for unpublished data, which they apparently did not have.

We included only studies meeting the three following preset criteria: studies restricted to the effect on bone mass of TH therapy; controlled cross-sectional studies (patients compared to a control group more or less carefully matched for age, sex, and menopausal status at least, unless z-scores calculated from a database were used; nested case-control studies inside cohort surveys were considered *a priori* to be well matched), and numerical data available for both patients and controls (number of patients, mean BMD ± SD or z-score). Studies about endogenous hyperthyroidism were excluded *a priori*, as were the few small and short term longitudinal studies (low exposure to TH) and studies with large numbers of patients receiving estrogen replacement therapy or with postoperative hypoparathyroidism unless separate data were available. In addition, a group or subgroup of patients inside a given study was considered to be receiving suppressive therapy when it met at least one of the following criteria: TSH level below the normal range for the assay used in at least 70% of the subjects from the given group (ultrasensitive RIAs were used in all studies), suppressed response to TRH test in at least 70% of patients, and, when none of these data was available, mean daily dose of T_4 (or equivalent) greater than 200 μg. Thus, for suppressive therapy, we applied more stringent criteria than those set by some authors. This definition led to a reclassification of some so-called suppressive studies into our replacement group to select studies that effectively resulted in suppressed TSH and to assess specifically their impact on bone.

We screened 48 studies dealing with the effects on bone of TH therapy. Seven studies (representing 246 patients) did not meet our inclusion criteria and were excluded *a priori*: 5 longitudinal studies (31–35), 1 study without bone mass measurements (36), and 1 with no control group (37). Eight (representing 482 patients) could not be included in our meta-analysis because some data were missing: numerical data lacking in 3 studies (38–40), no stratified data for pre- and postmenopausal women in 4 studies (41–44), and 1 abstract obtained too late to be included (45). Finally, 33 studies, comprising all but 1 (38) of the studies analyzed by Faber and Galloe, could be included (9, 22, 46–77) after additional data were obtained from 9 of the 21 authors to whom we wrote (49, 52, 53, 56, 60, 67, 72, 73, 76). Considering the effect of menopause on bone mass, and the various percentages of cortical and trabecular bone in the 6 anatomical sites studied, we decided to stratify the data according to sex, menopausal status, suppressive or replacement TH therapy, and anatomical site (lumbar spine, femoral neck, greater trochanter, Ward's triangle, and proximal and distal radius). This approach led us to perform 25 distinct meta-analyses on homogeneous subsets of patients (24 on women and 1 on men).

Statistics used for meta-analysis

The techniques used to measure bone mass varied greatly among studies and sites. Results were expressed in various units: bone mineral content (grams per cm^3), BMD (grams per cm^2), z-score, percentage of control value, and hydroxyapatite equivalent. From now on, we shall use the term bone mass when we do not refer to a specific technique. To allow their pooling, the results of each study were converted into a treatment effect size (standardized difference) with its confidence interval (CI), in accordance with Hedges and Olkin's method designed for quantitative data (29, 30). We used the fixed effect model because it allowed more precise estimates of overall effect sizes, thus lowering type 2 error. To determine whether pooling of data from all studies into an overall estimate was appropriate, a Q test for homogeneity was first performed on each subset meta-analysis. Provided homogeneity was present, an overall treatment effect size was calculated for each meta-analysis, with the results of each study being weighted according to the inverse of its variance. Thus, this weight depended on patient number and, to a lesser extent, the effect size itself (see *Appendix*). Studies were not weighted according to their quality assessment score, an insuperable task in our opinion in this case. The ratio of the overall effect size to its SD was used to test the probability of the null hypothesis, assuming a normal distribution of effect sizes. To compare the effects of suppressive and replacement therapies, the difference in overall effect sizes was divided by its SE, and its probability was assessed (z test, asymptotically following a normal law). All statistics used two-tailed tests, which were regarded as significant when $P < 0.05$. The extent of publication bias was examined by means of a funnel plot, in which the sample size of each subset of patients was plotted against its effect size, assuming that large studies (the apex of the plot) were less subject to publication bias and gave a better estimate of the overall effect size (Fig. 1).

Results

Main characteristics of the studies

Thirty-three studies remained eligible for the meta-analysis (9, 22, 46–77) (see Table 1), representing 138 subsets of

TABLE 1. List of studies included in our meta-analysis

Ref. No.	First author	Suppressive therapy									Replacement therapy					
		Men			Premenopausal			Postmenopausal			Premenopausal			Postmenopausal		
		n	Age (yr)	Duration (yr)	n	Age (yr)	Duration (yr)	n	Age (yr)	Duration (yr)	n	Age (yr)	Duration (yr)	n	Age (yr)	Duration (yr)
46	Abugassa, 1993							13	58.0	13.0						
47	Adlin, 1991							19 (7)	60.9	>5						
48	Campos, 1993										15		>1	9		>1
49	Chabert, 1990				8	44.8	8.0	20	57.0	8.0						
50	Demeester, 1990										7	28	3.8			
51	Diamond, 1991				14	41.6	10.7	10	59.0	5.9						
52	Eulry, 1992	23	45.5	6	16		6.0	4		6.0						
53	Florkowski, 1993	6			20		9.6	18		9.6						
54	Franklyn, 1992	5	56.8	7.9	18	41.1	7.7	26	63.4	8.1						
55	Franklyn, 1994										27 (27)	43.3	5.8	60 (60)	61.8	9.8
55	Franklyn, 1994													22	64.8	5.9
56	Gam, 1991							15	63.0	4.8				14	60.0	7.0
57	Garton, 1994				20	38.1	4.0				20	43.3	4.0			
58	Giannini, 1994				12	41.1	9.3	13	57.6	6.0						
59	Gonzalez, 1991	5	33.4	11.8	16	34.7	8.3	34	60.3	7.8						
60	Grant, 1993							44	64.6	12.6				34	63.6	10.3
61	Greenspan, 1991							28 (4)	61	15.0	28 (4)	44	12.0			
62	Hawkins, 1994							21	59.6	6.2				10	54.6	9.0
63	Kung, 1991										26	32.8	7.5			
64	Kung, 1993							34	62.0	12.2						
65	Lehmke, 1992	9	51.0	5.0	25		5.0	16		5.0						
66	Leprat, 1992	22		4.5	36		4.5	12		4.5						
67	Marcocci, 1993				47	39.0	10.1	17		8.6						
69	Matteucci, 1991				15	42	8.0									
70	Müller, 1992				23			27								
71	Paul, 1988										31	36.5	9.6			
72	Radetti, 1993				11		2.9				9		2.9			
9	Ross, 1987				28		>5									
73	Schneider, 1991	12	37.5	5.1	25	36.7	5.1									
22	Schneider, 1994							14		20.4				89		20.4
74	Stall, 1990							10	60.0	14.2						
75	Stêpàn, 1992	13	58.2	4.6	20	40.4	6.0	25	60.4	7.4						
76	Taelman, 1990										36	39.5	5.8	24	57.9	10.0
77	Wenzel, 1992				31	38.9	>5									
Total before exclusions		95	47.2	5.6	385	39.3	7.0	420	61.1	9.7	199	39.3	7.2	262	61.4	13.1
Total after exclusions		95	47.2	5.6	385	39.3	7.0	409	61.1	9.6	168	38.4	7.3	202	61.2	14.1

n, Number of patients. Mean age and mean duration of therapy (in years) are presented whenever available after our multiple stratification. The number of subjects excluded for previous history of endogenous hyperthyroidism is given in *parentheses*.

data according to our multistratified design, including 95 men and 1266 women (584 pre- and 682 postmenopausal). Twenty-seven studies could be considered at least in part to administer suppressive therapy according to our criteria (9, 22, 46, 47, 49, 51–54, 56–62, 64–67, 69, 70, 72–75, 77). Thus, the suppressed group was composed of 95 men and 805 women [385 premenopausal (mean age, 39.3; mean duration of therapy, 7.0 yr) and 420 postmenopausal (mean age, 61.1; mean duration of therapy, 9.7 yr)]. Thirteen studies were considered to deal at least partly with the effects of replacement therapy (22, 48, 50, 55–57, 60–63, 71, 72, 76), representing 461 women (199 premenopausal and 262 postmenopausal). For women, the most studied sites were, in decreasing order, lumbar spine (L1–L4; 26 studies; 1014 patients), femoral neck (17 studies; 714 patients), greater trochanter (10 studies; 483 patients), Ward's triangle (10 studies; 476 patients), distal radius (10 studies; 404 patients), and proximal radius (9 studies; 398 patients). Techniques of bone mass measurement were (in order of decreasing use) dual energy x-ray absorptiometry (11 studies; 1953 examinations), single photon absorptiometry (9 studies; 710 examinations), dual photon absorptiometry (14 studies; 710 examinations), and quantitative computerized tomography (4 studies; 116 examinations). Dual energy x-ray absorptiometry and dual photon absorptiometry were used for lumbar spine and hip, single photon absorptiometry was used for radius, and quantitative computerized tomography was used for all sites. To assess the validity of our decision to stratify, we first performed a multivariate analysis including all women. This regression analysis found that suppressive or replacement therapy, menopausal status, and percentage of trabecular bone (*i.e.* the anatomical site) each contributed significantly to the overall effect size (for the latter, r = 0.2 and $P = 0.04$). Conversely, the technique of bone mass measurement had no influence, thus allowing us to pool studies using various techniques. Elsewhere, the funnel plot (sample size of each study *vs.* its effect size) was symmetrical (Fig. 1), suggesting that there was no major publication bias in the studies we selected, as bigger studies gave an unbiased estimate of the various effect sizes of smaller ones.

Findings

The initial multistratified meta-analysis showed heterogeneity at some sites and for some subsets of data. We then tested several plausible hypotheses to reduce heterogeneity. We found that exclusion of the 102 women (31 premenopausal and 71 postmenopausal) with a history of primary hyperthyroidism from 3 studies considerably improved homogeneity (47, 55, 61). This exclusion was possible because separate data were available for all 3 subgroups of patients. Conversely, neither the ethnic origin of patients nor the type of TH used (T_4 *vs.* T_3) contributed to heterogeneity. However, this finding was not surprising because only 3 studies included non-Caucasians (47, 63, 64) and only 3 reports had a majority of patients treated with T_3 or T_3 plus T_4 (66, 75, 76). Our final meta-analysis involved 138 subsets of data (96, including 7 male subsets for suppressive and 42 for replacement therapy), representing 83 men and 1164 women [553 premenopausal (mean age, 39.1; mean duration of therapy, 7.2 yr) and 611 postmenopausal (mean age, 61.1; mean duration of therapy, 11.1 yr)], with a total of 3184 examinations (1899 for suppressive and 1285 for replacement therapy).

For suppressive therapy (see Tables 2 and 3), the final meta-analysis included 83 men, 794 women [385 premenopausal (mean age, 39.3 yr; mean duration of therapy, 7.0 yr)

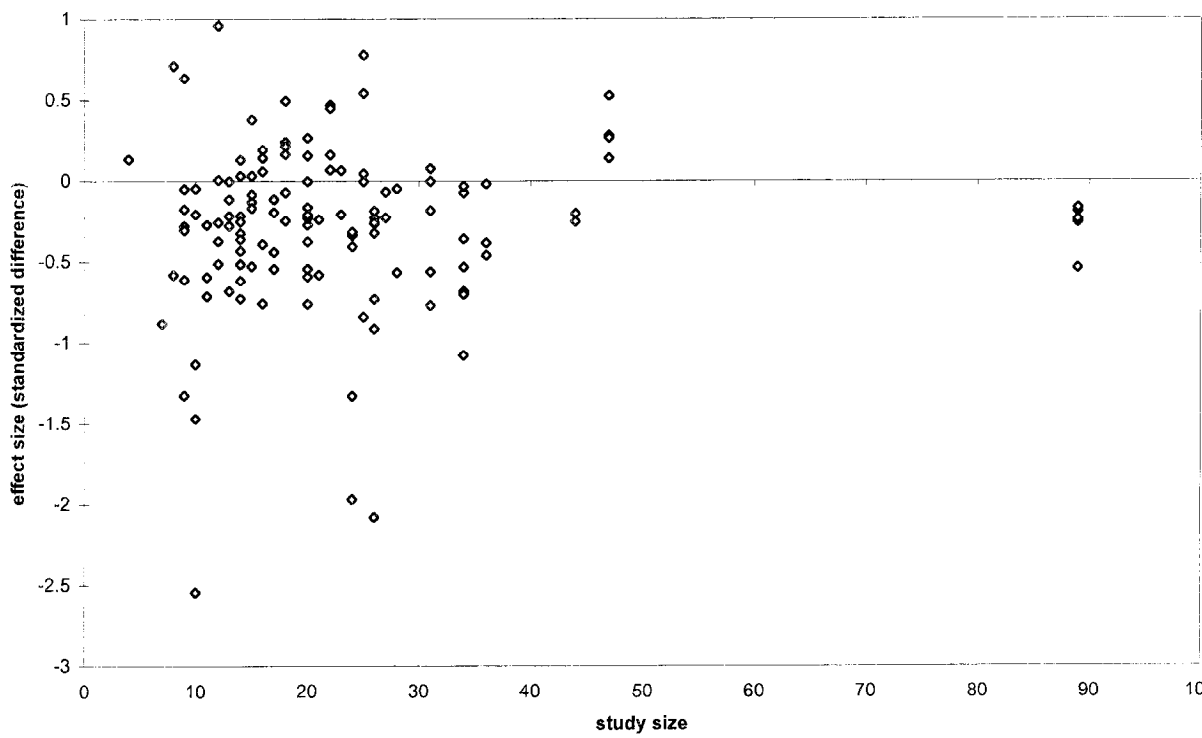

FIG. 1. The funnel plot of effect size *vs.* number of examinations in each subset (study size).

TABLE 2. Summary of results

Therapy	Sex/menopausal status	Anatomical site	No. of subsets	No. of BMD measurements	Homogeneity	Effect size	95% confidence interval		*P* value
Suppressive	Men	Lumbar spine	7	83	Yes	0.082	−0.238	0.401	0.62
Suppressive	Premenopausal women	Lumbar spine	13	275	Yes	0.231	0.063	0.398	0.007
		Femoral neck	6	142	Yes	0.020	−0.253	0.214	0.87
		Greater trochanter	3	85	Yes	0.052	−0.250	0.353	0.74
		Ward's triangle	3	85	Yes	0.134	−0.168	0.435	0.39
		Distal radius	5	106	Yes	0.029	−0.254	0.313	0.84
		Proximal radius	5	104	Yes	−0.178	−0.441	0.085	0.18
	Total for premenopausal women, suppressive therapy		35	797					
	Postmenopausal women	Lumbar spine	20	366	Yes	−0.348	−0.494	−0.202	<0.0001
		Femoral neck	12	220	No	−0.276	−0.470	−0.089	
		Greater trochanter	6	116	Yes	−0.484	−0.746	−0.222	0.0003
		Ward's triangle	6	116	Yes	−0.386	−0.595	−0.075	0.012
		Distal radius	6	106	Yes	−0.328	−0.601	−0.055	0.018
		Proximal radius	4	95	Yes	−0.448	−0.737	−0.159	0.002
	Total for postmenopausal women, suppressive therapy		54	1019					
	Total for women for suppressive therapy		89	1816					
Replacement	Premenopausal women	Lumbar spine	6	131	Yes	−0.295	−0.540	−0.050	0.018
		Femoral neck	5	116	Yes	−0.545	−0.808	−0.282	<0.0001
		Greater trochanter	3	77	No	−0.941	−1.282	−0.600	
		Ward's triangle	3	61	Yes	−0.481	−0.844	−0.118	0.009
		Distal radius	2	45	Yes	−0.327	−0.696	0.043	0.083
		Proximal radius	3	52	Yes	−0.498	−0.839	−0.157	0.004
	Total for premenopausal women, replacement therapy		22	482					
	Postmenopausal women	Lumbar spine	5	144	Yes	−0.125	−0.358	0.108	0.29
		Femoral neck	4	134	Yes	−0.106	−0.346	0.134	0.39
		Greater trochanter	2	111	No	−0.105	−0.370	0.159	
		Ward's triangle	3	120	Yes	−0.209	−0.463	0.046	0.11
		Distal radius	3	147	No	−0.407	−0.634	−0.180	
		Proximal radius	3	147	No	−0.641	−0.874	−0.409	
	Total for postmenopausal women, replacement therapy		20	803					
	Total for women for replacement therapy		42	1285					
Overall			131	3101					

Homogeneity between studies means a value less than 3.84 for Q-test ($P > 0.05$). The *P* value (*last column*) refers to the statistical significance of effect size.

and 409 postmenopausal (mean age, 61.1 yr; mean duration of therapy, 9.6 yr)]. Hip and spine were the most studied sites, as expected, as the burden of osteoporosis is primarily caused by fractures at these two sites. Men were analyzed separately; the spine was usually the only site measured (7 subgroups, 83 patients). There was no heterogeneity between subgroups of men and no effect of TH on bone mass. For premenopausal women, homogeneity was present at all sites, and TH had no significant effect, except for the spine, where TH had a paradoxical beneficial effect (combined effect size = 0.23; $P = 0.007$). For postmenopausal women, we found both homogeneity and a detrimental effect at all sites, including lumbar spine (see Fig. 2), except the femoral neck, where a single study with a marked detrimental effect induced heterogeneity (see Fig. 3). An overall detrimental effect persisted despite exclusion of this study from this meta-analysis.

For replacement therapy (see Tables 2 and 3), our final meta-analysis included 370 women [168 premenopausal (mean age, 38.4 yr; mean duration of therapy, 7.3 yr) and 202 postmenopausal (mean age, 61.2 yr; mean duration of therapy, 14.1 yr)]. Due to the much smaller numbers of subsets and patients, the lumbar spine and femoral neck were the only sites where we could conclude reliably that there was a significant detrimental effect in premenopausal women (6 subgroups and 131 patients for spine; 5 subgroups and 116 patients for femoral neck). We found no effect of TH in postmenopausal women for spine, femoral neck, or Ward's triangle (3 subgroups; 120 patients). Suppressive therapy was significantly more detrimental than replacement therapy to spine and hip in postmenopausal, but not in premenopausal, women. A summary of the outcomes of the 24 meta-analyses performed in women is given in Table 3.

Lowering the type 1 error (*i.e.* threshold for statistical

TABLE 3. Overview of results

Therapy/menopausal status	Spine (L2-L4)	Hip			Radius	
		Femoral neck	Greater trochanter	Ward's triangle	Proximal	Distal
Suppressive therapy						
Men	=					
	7/83					
Premenopausal women	+	=	=	=	=	=
	13/275	6/142	3/85	3/85	5/106	5/104
Postmenopausal women	−	?(−)	−	−	−	−
	20/366	12/220	6/116	6/116	6/106	4/95
Replacement therapy						
Premenopausal women	−	−	?(−)	−	−	=
	6/131	5/116	3/77	3/61	2/45	3/52
Postmenopausal women	=	=	?(=)	=	?(−)	?(−)
	5/144	4/134	2/111	3/120	3/147	3/147

+, Beneficial effect; −, detrimental effect; =, no effect; ?, heterogeneity (and, in *parentheses*, the tendency of result). Values are the number of studies/number of subjects.

significance) to account for the high number of tests performed (n = 25), although debatable, would not change our main results, because our *P* values were usually far below 0.05 (see Table 2). Similarly, the use of a random effect model, making no assumptions on the distribution of effect sizes among studies in the few subset meta-analyses in which heterogeneity was present using the fixed effect model, would bring no additional information, turning our inability to conclude into a no effect conclusion due to the wide CIs (data not shown).

Discussion

Our meta-analysis included all published studies except 1. The annual number of cross-sectional studies did not change between 1990 and 1994, with progressively fewer studies showing TH-induced bone loss. There was a global consistency between the results of our 25 meta-analyses at various anatomical sites and for various subgroups of patients. TH-suppressive therapy had a significant detrimental effect on all sites (including spine and femoral neck) in postmenopausal women, with no significant difference between suppressive and replacement therapies. These findings suggest a synergism between the bony effects of TH and estrogen deficiency. In a large cross-sectional study, the use of estrogens was associated with less TH-induced bone loss (22). The beneficial effect on spine of TH-suppressive doses in premenopausal women is difficult to explain. One could conceive of a positive effect of TH replacement therapy in premenopausal women in light of both the many undertreated hypothyroid patients and histomorphometric data from patients with untreated hypothyroidism that showed increased cortical width and decreased cortical porosity (6). Replacement therapy had a detrimental effect on the spine and femoral neck in premenopausal women, whereas it had no effect in postmenopausal women. Conclusions drawn from our meta-analyses of suppressive therapy should be more reliable, because we adopted stringent criteria for TSH suppression, and replacement therapy was only defined *a contrario*.

As almost all studies included only Caucasians, the ethnic origin of patients was not a confounding factor in our meta-analysis (78). Similarly, we could not test the influence of gender on the effect of TH on bone because our population included almost exclusively women. Conversely, the exclusion of all three subgroups of patients with a history of hyperthyroidism considerably improved *Q* tests for homogeneity. Our meta-analysis indirectly confirmed the deleterious effect of this factor already suspected from several (14, 41, 47, 55, 61) studies, but not all (22). Although the *Q* test usually concluded to homogeneity, it became clear from our meta-analysis that conflicting conclusions of the various cross-sectional studies probably resulted from their multiple uncontrolled sources of heterogeneity. A few factors known to influence bone mass were taken into account when matching controls with cases in almost all studies [gender, menopausal status, mean age of patients (and controls), absence of estrogen replacement therapy and oral contraception, and no intake of drugs interfering with calcium and/or bone metabolism], but many other risk factors (with varying impact and prevalence) were usually not matched [mean age at menarche, mean age at menopause (early onset is a risk factor for bone loss), smoking habits (79), alcohol intake (78), caffeine intake (14), calcium dietary intake, physical activity (14), tall stature, and body weight (excess weight correlates with decreased bone loss and risk for hip fractures)] (14, 79). Interestingly, studies not matching controls for weight were more prone to contribute to heterogeneity (5 of 5 *vs.* 15 of 28; $P = 0.06$, by one-tailed Fisher's exact test). The mean duration of TH therapy, mean dose, nature of underlying thyroid disease (total thyroidectomy, usually for cancer, is associated with calcitonin deficiency and sometimes with iatrogenic hypoparathyroidism), mode of recruitment of controls, technique of bone mass measurement, and various proportions of cortical and trabecular bone at each site are yet other potential sources of clinical heterogeneity. No cross-sectional study could control simultaneously for all of these factors. In addition, in a French study of spine BMD in 2279 women referred to a menopause clinic, all known risk factors for bone loss accounted for only 25% of BMD variance, suggesting a major role of unidentified genetic and environmental factors (43).

There is no simple method to assess the statistical validity of a meta-analysis. For the most studied sites (lumbar spine and femoral neck), we made the following simulations.

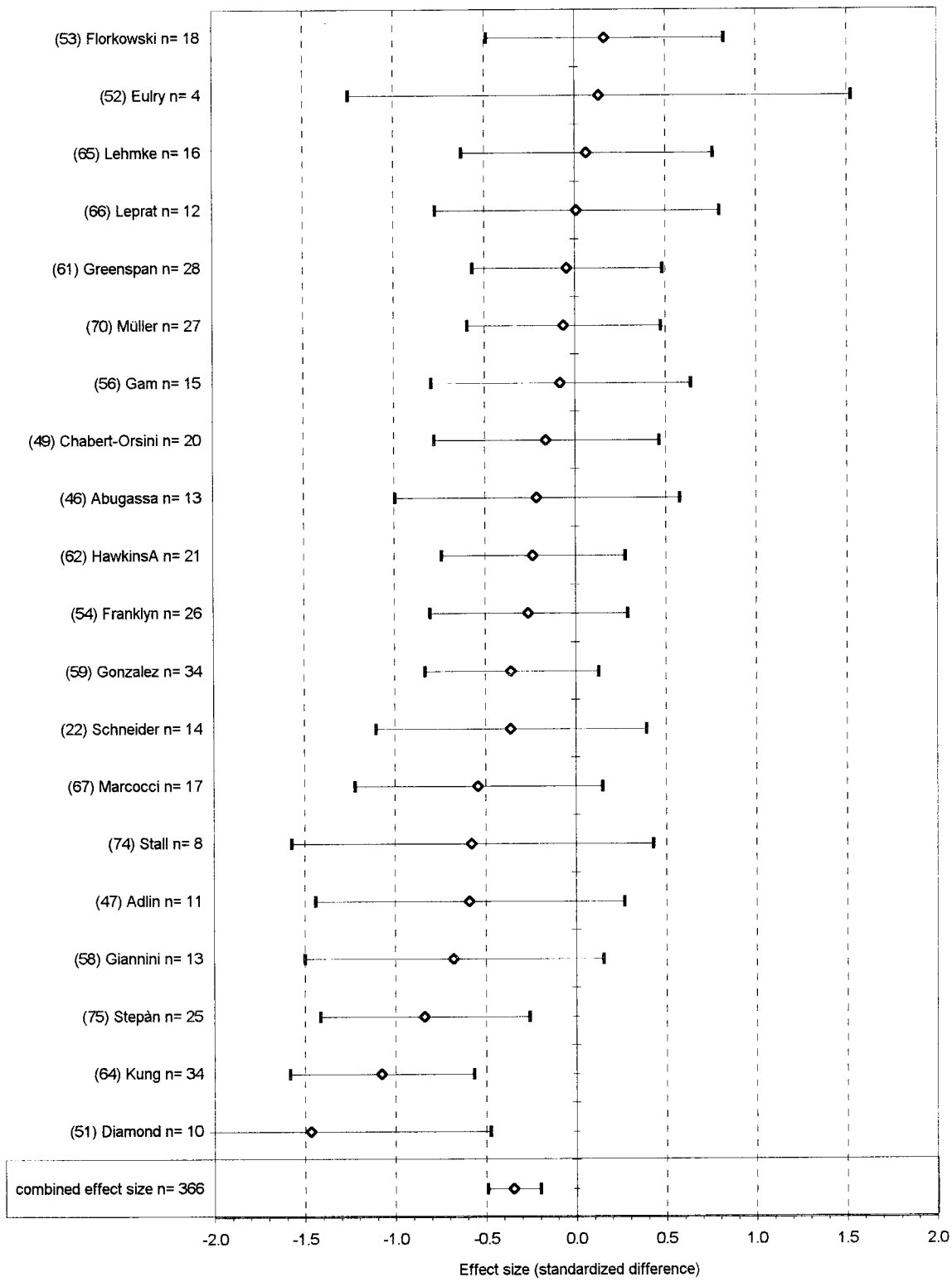

FIG. 2. Meta-analysis of studies concerning effects on the lumbar spine of suppressive TH therapy in postmenopausal women. Each study is visualized by its effect size with its 95% CI. The *last line* shows the combined effect size.

When we identified a significant detrimental effect, we computed how many times the study with the most beneficial effect would have to be duplicated to suppress the statistical significance of the overall effect and then to obtain a significant bone gain. We made symmetrical calculations for the only meta-analysis showing a beneficial effect of TH. When we found no significant effect, we computed how many times the study with the most detrimental effect would have

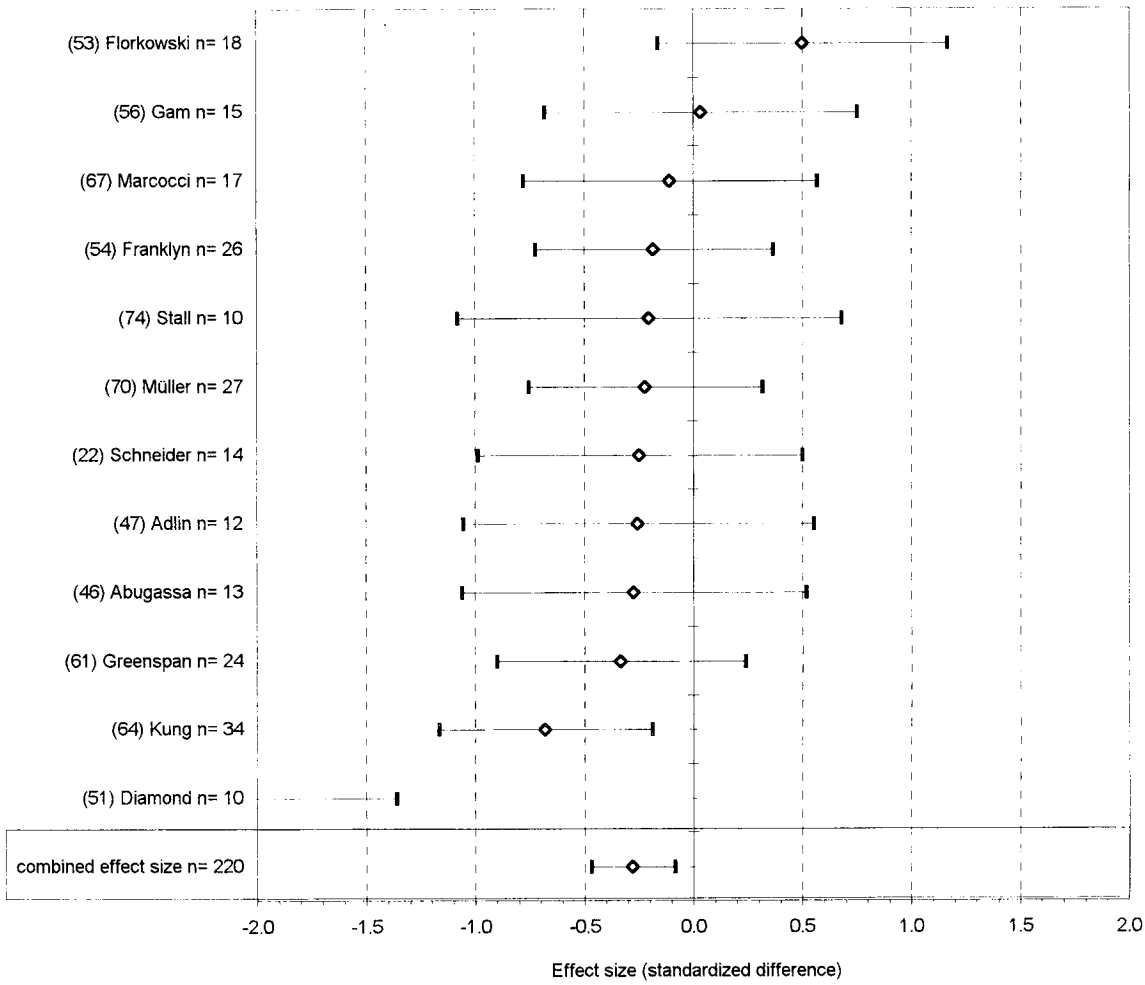

FIG. 3. Meta-analysis of studies concerning effects on femoral neck of suppressive TH therapy in postmenopausal women. Each study is visualized by its effect size with its 95% CI. The *last line* shows the combined effect size.

to be duplicated to obtain a significantly deleterious global effect and how many times the study with the most beneficial effect would have to be duplicated to obtain a significant gain in bone mass (see Table 4). A small number (from 1–18) of unpublished studies with diverging results (the publication bias) would change the findings of many of our 25 meta-analyses, except for the detrimental effect of suppressive therapy on the spine of postmenopausal women, for which 18 unfavorable studies would be needed to neutralize our conclusion (and 82 to reverse it). This greater robustness can be explained by the larger number of studies (n = 20), with a strong majority showing a trend toward a detrimental effect. As expected, the number of studies needed to reverse the findings would be much higher, ranging from 5–82.

TABLE 4. "Power" calculation

Therapy/site	Menopausal status	Actual results	No. of studies with the average no. of 20 subjects needed to modify results	
Suppressive therapy				
Spine	Pre	+	=:2	−:18
	Post	−	=:18	+:82
Femoral neck	Pre	=	−:3	+:10
	Post	−	=:2	+:13
Replacement therapy				
Spine	Pre	−	=:1	+:11
	Post	=	−:1	+:5
Femoral neck	Pre	−	=:2	+:8
	Post	=	−:6	+:15

+, Beneficial effect; −, detrimental effect; =, no effect.

Faber and Galloe (27) chose to pool all studies, leading to results that are difficult to interpret. As each study included various numbers of sites, a major criticism of this global approach would be the overweighting of studies measuring several sites, as each of their patients would be included several times, which does not comply with a fundamental rule of meta-analysis. Consequently, that approach would alter the percentages of men, pre- and postmenopausal women, and suppressive or replacement therapy (although the authors limited their analysis to suppressive therapy) and would lead to measurements of the effects of TH on a virtual bone, whose composition does not result from anatomical criteria but from the number of BMD measurements available for each site in the literature. Only this global pooling of data allowed Faber and Galloe to conclude that there was a

significant detrimental effect, as they did not find a significant effect at any individual site (27). Conversely, we chose *a priori* to stratify the data according to sex, menopausal status, suppressive or replacement therapy (hypothesizing a dose-effect relationship), and anatomical site (postulating differential effects of TH on cortical and trabecular bone). Therefore, the meta-analytic approach of the available data is confronted with an unsolvable dilemma; perform either a multiple stratification, leading to several empty squares (our choice), or a global pooling (Faber's choice), leading to questionable conclusions without a systematic gain in statistical power.

In our meta-analysis, the expression of results as effect size (*i.e.* standardized difference) allowed us to pool studies using various units of bone mass, but the combined effect size has no clinical meaning. Therefore, we applied our results to the large survey by Cummings *et al.* (12) to assess the predictability of hip fracture from BMD measurements at various sites in about 9000 postmenopausal white women. Our pooled results could then be expressed as percentages of bone loss. For suppressive therapy in postmenopausal women, the statistically significant detrimental effect we found represented 7% of the spine BMD (CI, 4–10%), 5% of the femoral neck BMD (CI, 2–8%), 9% of the trochanter and Ward's triangle BMDs (CI, 4–13% and 2–15%, respectively), and 7% of the distal radius BMD (CI, 1–13%). For premenopausal women, our findings represented a bone loss of 3% of spine and 7% of femoral neck BMDs (80). These relatively small bone losses (<10%) must be interpreted cautiously, for instance in terms of fracture risk. However, a 10% bone loss over a period of 10 yr may confer a 44% increase in the risk of hip fracture, and a 6% reduction of bone density (similar to what we found) might increase the lifetime risk of hip fracture to 12% (10). The risk of hip fracture increased 2.6 times for every decrease of 1 SD in the femoral neck and trochanter BMDs (12). The relative risk of spine fracture increased 1.5- to 2-fold for a 1 SD decrease in BMD or a 10% decrease in *t*-score (80). Therefore, we concluded that, at least in postmenopausal women, TH-suppressive therapy probably has a detrimental effect on bone mass, but we cannot say that it induces osteopenia because our detrimental effects were usually less than 0.5 SD. However, as the association between BMD and fracture risk is exponential and the use of TH is so common, our findings may have public health implications because they result in an increased theoretical risk of fracture of 1.6 for both hip and lumbar spine in postmenopausal women. Conclusions must be drawn cautiously from our meta-analysis, since it has several limitations. Firstly, the studies we pooled were cross-sectional, and confounding factors were often poorly controlled. Secondly, our conclusions for many sites are not very robust, because stratification scattered the data. Thirdly, the detrimental effect was found mainly in postmenopausal women and, although statistically significant, never exceeded 1 SD (or 10% of the bone mass) and exceeded 0.5 SD only once. Despite these limitations, our meta-analysis found that TH-suppressive therapy consistently had a mild, but statistically significant, detrimental effect on bone density in postmenopausal women. Overtreatment with TH probably contributes to the development of osteoporosis in postmenopausal women. Despite its relatively low impact on bone loss, this effect of TH is worth considering because it should be avoidable at least in part with closer follow-up of TSH and restricting suppressive therapy to thyroid cancer patients. We found a detrimental effect on both spine and hip, the major sites of osteoporotic fractures, but bone loss is not the only determinant of fractures, and the clinical relevance of TH-induced marginal bone loss (~0.5 SD in our meta-analysis) remains to be fully established.

TH exert a dual effect on bone. Physiological levels are required for bone maturation, but hormone excess increases bone turnover and reduces bone mass. How exactly TH regulate bone remodeling remains unclear. *In vitro* data showed that T_3 (at levels found in hyperthyroidism) suppressed the differentiation of osteoprogenitor cells into osteoblasts, but enhanced the functional activity of mature osteoblasts (81). TH act indirectly on bone resorption by osteoclasts (82), presumably via cytokines and growth factors. Nuclear T_3 receptors have been demonstrated in osteoblast cell lines. The percentage of trabecular bone differs markedly between anatomical sites, representing more than 67% for lumbar spine (83, 84), 50% for femoral trochanter, 25% for both femoral neck and Ward's triangle (83, 84), and 0–5% and 20–40% for midshaft and distal radius, respectively (85). Pathological bone loss affects mainly trabecular bone, probably because of its higher surface to volume ratio and its greater remodeling activity. However, experimentally, TH seem to affect cortical bone more severely (4–6). Our meta-analysis is the first clinical study to corroborate biopsy data showing a predominantly cortical effect of TH, as we found a low, but significant, positive correlation between the amount of cortical bone at various sites and the corresponding bone loss (data not shown).

Additional cross-sectional studies will bring no further insight to the issues raised. Their design is not appropriate, because the many risk factors for bone loss do not allow correct matching of controls with cases. An epidemiological approach to risk factors for hip fractures has already been more fruitful. A cross-sectional study did not find an increased risk of overall fracture or more fractured femoral necks or spines or forearms among white postmenopausal women treated with L-T_4 (86). Similar results were found in a series of 1180 patients receiving L-T_4 regardless of whether their TSH was suppressed, with a trend toward an increased overall fracture rate in the subgroup of patients over 65 yr of age with suppressed TSH (25). In the former study, prior thyrotoxicosis was associated with an earlier occurrence of fractures (86). A recent case-control study found that a history of hyperthyroidism (but not TH therapy) was associated with an increased risk of hip fractures (23). These discrepancies between retrospective studies might result from various periods of follow-up and biases. Recently, a prospective study of 9500 women aged 65 yr or older (mean follow-up, 4.1 yr) found an increased risk of hip fractures among women with a past history of endogenous hyperthyroidism (relative risk, 1.8), but no specific risk in women taking TH therapy (14). Femoral BMD did not account for the strong association between previous hyperthyroidism and risk of hip fracture, suggesting a prolonged impairment of bone strength by hyperthyroidism, not detected by densitometry, or an impair-

ment of muscular strength. Only long term longitudinal prospective studies, focusing on BMD measurements (and ideally on the meaningful clinical end point of fractures), will help to further address these issues. A large, double blind, placebo-controlled trial, to test the effect of TH-suppressive therapy on the growth of benign nodules and to look for a deleterious effect on bone, would be a major advance. Because 1 cycle of bone remodeling lasts more than 6 months, each patient should receive TH-suppressive therapy for at least 2 yr. Based on our data, such a trial should include 150–300 postmenopausal women in each group to detect a significant effect on BMD ($P < 0.05$) with a statistical power of 0.8. Pending completion of such study and considering our results, the TH dose should be carefully titrated, especially whenever replacement therapy is needed and the TSH level is below normal values; the L-T_4 dose should be progressively decreased until TSH rises to values within the normal range, with each step lasting at least 1 month due to the long half-life of T_4. Overzealous or irrelevant TH prescriptions should be avoided.

Appendix: Steps of Calculation

The following data were taken from the studies by Whitehead and Whitehead (30) and Hedges and Olkin (29).

Preliminary definitions

For each of the k studies the following data are available: m_{Ti}, s_{Ti}, and n_{Ti}, which are, respectively, the mean, SD and number of subjects in the thyroid hormone-treated group of the i^{th} study, and m_{Ci}, s_{Ci}, and n_{Ci}, which are, respectively, the mean, SD, and number of subjects in the control group of the i^{th} study.

Computing of the pooled sample SD for each trial:

$$s_i = \sqrt{\frac{(n_{Ti} - 1)s_{Ti}^2 + (n_{Ci} - 1)s_{Ci}^2}{(n_{Ti} + n_{Ci} - 2)}} \quad \text{(I)}$$

Computing of a therapy effect size, for each trial

$$\hat{\theta}_i = \frac{m_{Ti} - m_{Ci}}{s_i} \quad \text{(II)}$$

if the only data available are z-score, we entered the value of the z-score as $\hat{\theta}_i$; this approximation is improved if we use the estimate:

$$\hat{\theta}_i = J(n_{Ti} + n_{Ci} - 2)\frac{m_{Ti} - m_{Ci}}{s_i} \quad \text{(III)}$$

where the function J is approximated by:

$$J(n) = 1 - \frac{3}{(4n - 1)} \quad \text{(IV)}$$

Computing of an approximation of the variance of $\hat{\theta}_i$:

$$\sigma^2(\hat{\theta}_i) = \frac{n_{Ti} + n_{Ci}}{n_{Ti}n_{Ci}} + \frac{\hat{\theta}_i^2}{2(n_{Ti} + n_{Ci})} \quad \text{(V)}$$

and an approximate 95% CI for $\hat{\theta}_i$ is given by:

$$\theta_i = \hat{\theta}_i \pm 1.96 \cdot \sigma(\hat{\theta}_i) \quad \text{(VI)}$$

Computing of the weights for each study:

$$w_i = \frac{1}{\sigma^2(\hat{\theta}_i)} \quad \text{(VII)}$$

Computing of a combined estimate of the effect size from all of the k studies along with its variance:

$$\hat{\theta} = \frac{\sum \hat{\theta}_i w_i}{\sum w_i}$$
$$\text{var}(\hat{\theta}) = \frac{1}{\sum w_i} \quad \text{(VIII)}$$

and an approximate 95% CI for is given by:

$$\theta = \hat{\theta} \pm 1.96 \cdot \sqrt{\frac{1}{\sum w_i}} \quad \text{(IX)}$$

Homogeneity test

Testing the zero hypothesis (H0), that the k values of $\hat{\theta}_i$ are equal ($\hat{\theta}_1 = \hat{\theta}_2 = \ldots = \hat{\theta}_k$), a Q value is computed as:

$$Q = \sum w_i(\hat{\theta}_i - \hat{\theta})^2 \quad \text{(X)}$$

If H0 is true, Q tends toward a χ^2 distribution with $k - 1$ degrees of freedom as the sample size in each study becomes large. H0 is rejected if the Q value exceeds the $(1 - \alpha)$ critical value, with $\alpha = 0.05$.

Computing the test statistic for $\hat{\theta}$:

$$U = \frac{\hat{\theta}^2}{\text{var}(\hat{\theta})} = \frac{(\sum \hat{\theta}_i w_i)^2}{\sum w_i} \quad \text{(XI)}$$

which follows a χ^2 distribution with 1 degree of freedom under the null hypothesis, H0: $\hat{\theta} = 0$.

Computing the SE of the difference of two combined estimates $\hat{\theta}_m$ and $\hat{\theta}_n$:

$$SE_{diff} = \sqrt{\sigma^2(\hat{\theta}_m) + \sigma^2(\hat{\theta}_n)} \quad \text{(XII)}$$

provided the data are independent.

Computing the comparison of the difference of two combined estimates $\hat{\theta}_m$ and $\hat{\theta}_n$ to zero, provided the data are independent:

$$Z = \frac{|\hat{\theta}_m - \hat{\theta}_n|}{SE_{diff}} \quad \text{(XIII)}$$

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