Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

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Context Data regarding the association between subclinical hypothyroidism and cardiovascular disease outcomes are conflicting among large prospective cohort studies. This might reflect differences in participants' age, sex, thyroid-stimulating hormone (TSH) levels, or preexisting cardiovascular disease.

Objective To assess the risks of coronary heart disease (CHD) and total mortality for adults with subclinical hypothyroidism.

Data Sources and Study Selection The databases of MEDLINE and EMBASE (1950 to May 31, 2010) were searched without language restrictions for prospective cohort studies with baseline thyroid function and subsequent CHD events, CHD mortality, and total mortality. The reference lists of retrieved articles also were searched.

Data Extraction Individual data on 55,287 participants with 542,494 person-years of follow-up between 1972 and 2007 were supplied from 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan. The risk of CHD events was examined in 25,977 participants from 7 cohorts with available data. Euthyroidism was defined as a TSH level of 0.50 to 4.49 mIU/L. Subclinical hypothyroidism was defined as a TSH level of 4.5 to 19.9 mIU/L with normal thyroid hormone concentrations.

Results Among 55,287 adults, 3,450 had subclinical hypothyroidism (6.2%) and 51,837 had euthyroidism. During follow-up, 9,664 participants died (2168 of CHD), and 4,470 participants had CHD events (among 7 studies). The risk of CHD events and CHD mortality increased with higher TSH concentrations. In age- and sex-adjusted analyses, the hazard ratio (HR) for CHD events was 1.00 (95% confidence interval [CI], 0.86-1.18) for a TSH level of 4.5 to 6.9 mIU/L (20.3 vs 20.3/1000 person-years for participants with euthyroidism), 1.37 (95% CI, 0.96-1.94) for a TSH level of 7.0 to 9.9 mIU/L (23.8/1000 person-years), and 1.89 (95% CI, 1.28-2.80) for a TSH level of 10 to 19.9 mIU/L (n = 70 events/235; 38.4/1000 person-years; P < .001 for trend). The corresponding HRs for CHD mortality were 1.09 (95% CI, 0.91-1.30; 5.3 vs 4.9/1000 person-years for participants with euthyroidism), 1.42 (95% CI, 1.09-1.85; 6.9/1000 person-years), and 1.58 (95% CI, 1.10-2.27; n = 28 deaths/333; 7.7/1000 person-years; P = .005 for trend). Total mortality was not increased among participants with subclinical hypothyroidism. Results were similar after further adjustment for traditional cardiovascular risk factors. Risks did not significantly differ by age, sex, or preexisting cardiovascular disease.

Conclusions Subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.
(TSH) for treatment of subclinical hypothyroidism, defined as elevated serum TSH levels with normal thyroid hormone (T₄ and T₃) concentrations. Because subclinical hypothyroidism has been associated with hypercholesterolemia and atherosclerosis, screening and treatment have been advocated to prevent cardiovascular disease. However, data on the association with coronary heart disease (CHD) events and mortality are conflicting among several large prospective cohorts. Three recent study-level meta-analyses found modestly increased risks for CHD and mortality, but with heterogeneity among individual studies that used different TSH cutoffs, different confounding factors for adjustment, and varying CHD definitions. Part of the heterogeneity might also be related to differences in participants’ age, sex, or severity of subclinical hypothyroidism (as measured by TSH level). One cohort study suggested particularly high risk in participants with subclinical hypothyroidism and preexisting cardiovascular disease.

Analysis of individual participant data from large cohort studies may reconcile these conflicting data and define the influence of age, TSH levels, and preexisting cardiovascular disease. Individual participant data analysis is considered the best way for synthesizing evidence across several studies because it is not subject to potential bias from study-level meta-analyses (ecological fallacy) and allows performance of time-to-event analyses.

To clarify the cardiovascular risk of subclinical hypothyroidism, we formed the Thyroid Studies Collaboration and conducted an individual participant data analysis of subclinical hypothyroidism and CHD outcomes.

**METHODS**

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Identification of potential studies was based on protocols developed for our study-level meta-analysis of prospective cohort studies. Briefly, we conducted a systematic literature search of articles in all languages on the association between subclinical thyroid dysfunction and CHD or mortality (cardiovascular and total) published from 1950 to May 31, 2010, in the MEDLINE and EMBASE databases and searched bibliographies of key articles (details are available in the eMethods). To maximize the quality and comparability of the studies, we formulated general inclusion criteria a priori. We included only full-text, published longitudinal cohort studies that (1) measured thyroid function with both serum TSH level and thyroid hormone (T₄ level) at baseline in adults, (2) followed up participants systematically over time, (3) assessed CHD events and/or mortality, and (4) had a comparison group with euthyroidism. Possible studies for inclusion were independently assessed for eligibility by 2 of the authors (N.R., J.G.) and any disagreement was resolved by discussion with a third author (D.C.B.). The agreement between the 2 reviewers was 99.9% for the first screen (titles and abstracts, κ = 0.98) and 100% for the full-text screen (κ = 1.00).

Investigators from each eligible study were invited to join the Thyroid Studies Collaboration. We collected detailed information about prespecified outcomes and potential confounding variables for each participant. Requested data included individual demographic characteristics, baseline thyroid function (TSH and T₄ levels), baseline cardiovascular risk factors (eg, low- and high-density lipoprotein cholesterol level, diabetes, blood pressure, cigarette smoking), prevalent cardiovascular disease, medication use at baseline (thyroid medication, lipid-lowering and antihypertensive drugs), and outcome data.

To maximize the comparability of the studies, we used a common definition of subclinical hypothyroidism. Based on expert reviews and definitions used in the Cardiovascular Health Study, we defined subclinical hypothyroidism as a serum TSH level of 4.5 mIU/L or greater to less than 20 mIU/L, with a normal T₄ concentration; and euthyroidism was defined as a serum TSH level of 0.5 mIU/L or greater and less than 4.5 mIU/L. Because the Whickham Survey used a first-generation TSH radioimmunoassay, which gives higher measured TSH values than current assays, and the recent analysis of this study, a TSH range of 6.0 mIU/L or greater to less than 19.9 mIU/L was used for this individual participant data analyses, as in the original and recent analysis of this study. In that study, a serum TSH level of 6.0 mIU/L corresponded to the 97.5th percentile of the distribution of serum TSH levels in 2,054 participants without overt thyroid disease. A TSH range of 6.0 mIU/L or greater to less than 4.5 mIU/L gives higher measured TSH values than current assays. The Whickham Survey measured total T₄ levels. Participants with abnormal T₄ values, results suggestive of nonthyroidal illness (low TSH and FT₄ levels) or low TSH level (<0.5 mIU/L) were excluded (n = 3023). Some studies had participants with missing T₄ values; we considered participants with a TSH level of 4.5 mIU/L to 19.9 mIU/L and a missing T₄ level as having subclinical hypothyroidism because most adults with this degree of TSH elevation have subclinical and not overt hypothyroidism. We performed a sensitivity analysis excluding those with a missing T₄ level.

Outcome measures were CHD events, CHD mortality, and total mortality. To limit outcome heterogeneity observed with previous study-level meta-analyses, we used more homogeneous outcome definitions. Similar to the current Framingham risk score, we limited cardiovascular mortality to CHD mortality or sudden death. A CHD event was defined as nonfatal myocardial infarction or CHD death (equivalent to hard events in the Framingham risk score) and hospitalization for angina or coronary...
revascularization (coronary artery bypass grafting or angioplasty).6 We performed a sensitivity analysis with hard events only.

Using previously described criteria45 and new information from study authors, we systematically evaluated the following key indicators of study quality52: methods of outcome adjudication and ascertainment, accounting for confounders, and completeness of follow-up ascertainment. Two reviewers (N.R., J.G.) rated all studies for quality.

We used separate Cox proportional hazard models to assess the associations of subclinical hypothyroidism with CHD events and mortality for each cohort (SAS version 9.2, SAS Institute Inc, Cary, North Carolina). Pooled estimates for each outcome were calculated using random-effects models based on the variance model according to DerSimonian and Laird,31 as recommended14,22 and published in recent 2-stage individual participant data analyses.85 Results were summarized using forest plots (Review Manager version 5.0,24 Nordic Cochrane Centre, Copenhagen, Denmark). The research authors of 1 study with 14 CHD outcomes53,66 declined to participate; as recommended,22 we included the published summary estimate from that study in the random-effects models in a sensitivity analysis. To assess heterogeneity across studies, we used the $P$ statistic, which describes the total variation across studies attributable to heterogeneity rather than chance ($P > .05$ indicating at least moderate statistical heterogeneity).55

Primary analyses were adjusted for age and sex, and then for traditional cardiovascular risk factors (systolic blood pressure, smoking, total cholesterol, diabetes) that were available in all cohorts (except for the Birmingham Study,23 which was excluded from this analysis). We considered the age- and sex-adjusted model as the primary analysis because some traditional risk factors are potential mediators of the relationship between subclinical hypothyroidism and CHD.4

To explore sources of heterogeneity, we performed several predefined subgroup and sensitivity analyses. We conducted stratified analyses by age, sex, race, TSH concentrations, and preexisting cardiovascular disease. Based on expert reviews2,6 and previous studies,25,26 subclinical hypothyroidism was stratified according to the following TSH concentration categories: 4.5-6.9 mIU/L (mild elevation), 7.0-9.9 mIU/L (moderate elevation), and 10.0-19.9 mIU/L (marked elevation). In the study-specific analyses stratified by age or TSH level, some strata had participants without either CHD deaths or CHD events (for 1 study27).

For these study-specific analyses, we used penalized likelihood methods27 to obtain hazard ratios (HRs) and confidence intervals (CIs). As done in previous studies,25,27,29 after including all participants in the primary analyses, we performed sensitivity analyses excluding participants who had thyroid hormone use at baseline (all excluded in 5 studies) and 0% to 12.6% reported thyroid hormone use during follow-up. The baseline (all excluded in 5 studies) and 0% to 12.6% reported thyroid hormone use during follow-up. The median follow-up ranged from 2.5 to 20 years, with total follow-up of 542,494 person-years.

To calculate age- and sex-adjusted rates per 1000 person-years, we first fit Poisson models25 to the pooled data, then standardized the fitted rate in the euthyroidism group to the overall age and sex distribution of the pooled sample. Finally, to obtain rates in the TSH groups consistent with the meta-analytic results, we multiplied the standardized rates in the euthyroidism group by the summary meta-analytic HRs. We checked the proportional hazard assumption using graphical methods and Schoenfeld tests (all $P > .05$). We used the Egger test35 and age- and sex-adjusted funnel plots to assess for publication bias.

**RESULTS**

| TABLE 1. Baseline Characteristics of Individuals in Included Studies (N=55 287) |

All 11 cohort studies reported total and CHD deaths, and 7 studies also reported CHD events among 25,977 participants. For the quality of individual studies, all studies reported outcome adjudication without knowledge of thyroid status; 4 of 7 studies reporting CHD events used formal adjudication procedures64,85,27, and 4 of 11 studies reporting CHD deaths mainly used death certificates.20,23,35 All studies had 5% or less loss to follow-up.
During follow-up, 9,664 participants died (2,168 of CHD) and 4,470 participants had CHD events (among 7 studies). In age- and sex-adjusted analyses, the overall HR for participants with subclinical hypothyroidism compared with euthyroidism was 1.18 (95% CI, 0.99-1.42) for CHD events (24.0 vs 20.3/1000 person-years for participants with euthyroidism), 1.14 (95% CI, 0.99-1.32) for CHD mortality (5.5 vs 4.9/1000 person-years), and 1.09 (95% CI, 0.96-1.24) for total mortality (23.1 vs 21.1/1000 person-years; Figure 1). We found heterogeneity across studies for CHD events ($I^2 = 59\%$) and total mortality ($I^2 = 66\%$), but not for CHD mortality ($I^2 = 0\%$). We subsequently examined whether heterogeneity was related to differences in risks by degree of subclinical hypothyroidism and age. The risk of CHD events ($P<.001$ for trend) and CHD death ($P=.005$ for trend) increased with higher TSH level, but not for total mortality (Figure 2). In stratified analyses, participants with TSH levels of 10 mIU/L or greater had significantly increased risk of CHD events (HR, 1.89 [95% CI, 1.28-2.80]; n = 70 events/235; 38.4 vs 20.3/1000 person-years for participants with euthyroidism) and CHD mortality (HR, 1.58 [95% CI, 1.10-2.27]; n = 28 deaths/333; 7.7 vs 4.9/1000 person-years) compared with participants with euthyroidism. The risk for CHD associated with subclinical hypothyroidism appeared to be somewhat higher in younger participants, but the number of outcomes in the younger age group was small, and there was no significant trend in CHD risk across age groups. Otherwise, the risk estimates for CHD events, CHD mortality, and total mortality did not differ significantly according to age, sex, race, or preexisting cardiovascular disease, except an increase in CHD events and CHD mortality among white but not among nonwhite participants with subclinical hypothyroidism (Table 2). All results were similar after further adjustment for traditional cardiovascular risk factors.

Figure 1. Subclinical Hypothyroidism vs Euthyroidism for Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality*

*The sizes of the data markers are proportional to the inverse variance of the hazard ratios (HRs). CI indicates confidence interval; HUNT, Nord-Trøndelag Health Study; HR, hazard ratio.

Figure 2. Hazard Ratios (HRs) for Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality According to Elevated Thyroid-Stimulating Hormone (TSH) Categories and Subclinical Hypothyroidism Stratified by Age vs Euthyroidism*

*The sizes of the filled square data markers are proportional to the inverse variance of the HRs. The unfilled squares indicate the reference categories. For the analyses stratified by age, the HRs for CHD events, CHD mortality, and total mortality were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata. CI indicates confidence interval.

Table 2. Stratified Analyses for the Associations Between Subclinical Hypothyroidism and Risk of Coronary Heart Disease (CHD) Events, CHD Mortality, and Total Mortality
Sensitivity analyses yielded similar results, with increased risks of CHD events and mortality in those with TSH levels of 10 mIU/L or greater (Table 3). Risk estimates were slightly higher for those with TSH levels of 10 mIU/L or greater after excluding those who took thyroid medication during follow-up. Estimates were lower for subclinical hypothyroidism overall after limiting the analyses to 4 studies with formal adjudication procedures, but slightly higher for those with TSH levels of 10 mIU/L or greater. The effect of increasing TSH level on CHD events did not significantly differ according to age ($P = .87$ for interaction). We found no evidence of publication bias, either with visual assessment of age- and sex-adjusted funnel plots or with the Egger test for mortality data ($P = .39$ for CHD mortality and $P = .97$ for total mortality) and little evidence of publication bias for CHD events ($P = .13$ for CHD events).

**Table 3.** Sensitivity Analysis of the Effect of Subclinical Hypothyroidism on the Risk of Coronary Heart Disease (CHD) Events and CHD Mortality

In this analysis of 55,287 individual participants from 11 prospective cohort studies, subclinical hypothyroidism was associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels. There was a significant trend of increased risk at higher serum TSH concentrations, and the risk of both CHD mortality and CHD events was significantly increased in participants with TSH levels of 10 mIU/L or greater. These associations persisted after adjustment for traditional cardiovascular risk factors, and did not significantly differ by age, sex, race, or preexisting cardiovascular disease. Compared with participants with euthyroidism, the overall HR for CHD events with subclinical hypothyroidism was 1.18 (95% CI, 0.99-1.42) and the overall HR for CHD mortality was 1.14 (95% CI, 0.99-1.32). Minimal TSH elevations were not associated with an increased risk of CHD events and CHD mortality. Our results clarify the CHD risk of subgroups of adults with subclinical hypothyroidism, which could not be adequately addressed in previous study-level meta-analyses or in single cohort studies performed in more limited age groups or without TSH stratification.

These results are generally consistent with previous study-level meta-analyses showing modest increased risks of CHD events and cardiovascular mortality associated with subclinical hypothyroidism. However, these meta-analyses could not accurately explore potential differences related to participant characteristics (eg, age, TSH concentrations) because of potential bias without individual participant data analysis (ecological fallacy), and they also were limited by clinical heterogeneity, with individual studies using varying TSH cutoffs, confounding factors for adjustment, and CHD definitions. Among 11 cohorts, only 2 studies previously reported results stratified by TSH level. One study reported an increased risk of CHD events in participants with a TSH level of 10.0 mIU/L or greater (HR, 2.22; 95% CI, 1.2-4.2) and the other study reported an increased risk of cardiovascular mortality (HR, 2.26; 95% CI, 0.54-9.45) but not CHD events (HR, 0.96; 95% CI, 0.35-2.61). Over 4 years among adults aged 70 to 79 years with TSH levels of 10 mIU/L or greater. However, the HR for CHD events increased to 1.28 (95% CI, 0.68-2.39) with extended follow-up to 8 years in the present data. In overall pooled data, we found statistical heterogeneity among individual study findings for CHD events ($P = .59$), but not for CHD death. Part of the heterogeneity might be related to different CHD risks across age, race, and TSH subgroups.
Our individual participant data analysis found that the CHD outcomes in adults with subclinical hypothyroidism did not differ significantly across age groups. For the specific age group of 80 years or older, there was a significant increased risk of total mortality, CHD mortality, or CHD events in contrast to a single previous study that found reduced mortality associated with increasing TSH concentrations. Previous study-level meta-analyses have found increased risks of CHD events and cardiovascular mortality associated with subclinical hypothyroidism, particularly in studies with a mean age of younger than 65 years, but this was not confirmed by our individual participant data analysis. We found some evidence for increased risks of CHD events and mortality in younger adults with subclinical hypothyroidism, but there also were large 95% CIs without significant trend across age groups (Figure 2). Moreover, the effect of increasing TSH level on CHD events did not significantly differ according to age. In contrast to a previous study suggesting that adults with subclinical hypothyroidism and preexisting cardiovascular disease might be at particularly high cardiovascular risk, we found no significant effect of baseline preexisting cardiovascular disease on outcomes.

The increased risk of CHD events associated with higher TSH levels in our study might be related to the known effects of thyroid hormone on the heart and metabolism, consistent with the concept that subclinical hypothyroidism is a milder form of overt hypothyroidism. Increased systemic vascular resistance, arterial stiffness, altered endothelial function, increased atherosclerosis, and altered coagulability have been reported to be associated with subclinical hypothyroidism and may accelerate development of CHD. The fact that adjustment for traditional cardiovascular risk factors did not alter risks could favor this hypothesis. Other potential mechanisms include elevated cholesterol level, although adjustment for cholesterol level did not remove the associations in our data. Adults with higher TSH concentrations also are more likely to develop overt hypothyroidism, and it is possible that this progression explains the association with subclinical hypothyroidism. Alternative explanations for the observed results are bias in the selection of included studies, bias and quality problems in the original studies, publication bias, and unmeasured confounders. Sensitivity analyses pooling higher-quality studies yielded similar results. Whereas one randomized controlled trial has shown benefits with thyroxine treatment of subclinical hypothyroidism on intima-media thickness and another has shown benefits with thyroid treatment of subclinical hypothyroidism on brachial artery endothelial function, the potential causal relationship can only be proven by randomized controlled trials of thyroxine replacement and clinical outcomes.

Among the strengths of our study, an individual participant data analysis is the preferred way to perform subgroup analysis and to allow standardization of definitions of predictors, outcomes, and adjustment for potential confounders. We included all available international and published data on these associations. Among the limitations of our study, the individual participant data analysis included predominantly white populations, except for 2 studies conducted in Japan and Brazil. Results for subgroups at risk of CHD mortality generally had wider 95% CIs than those for CHD events, reflecting less statistical power. However, post hoc calculations showed 80% power to detect meaningful differences between overall subclinical hypothyroidism and euthyroidism groups for each outcome. Specifically, our study had adequate power to detect an HR of 1.18 or higher for CHD events, an HR of 1.30 or higher for CHD mortality, and an HR of 1.13 or higher for total mortality. Even with this very large amount of individual participant data, our power for subgroup analyses was limited among those with TSH levels of 10 mIU/L or greater or adults younger than 50 years because of the limited number of CHD events and deaths. Thyroid function testing was performed only at baseline, and we have no data on how many participants progressed from euthyroidism to subclinical hypothyroidism, from subclinical to overt hypothyroidism, or who normalized their TSH level over time, which is a limitation of all published large cohorts. In addition, free triiodothyronine (T₃) was not available in most cohorts, and thus could not be included in thyroid status classification. Commencement of thyroid medication during follow-up by up to 12.6% of participants might have attenuated any true effects of subclinical hypothyroidism, as illustrated by the sensitivity analysis excluding such participants.

In summary, combining all available data from large prospective cohorts among 55,287 individual participants suggests that subclinical hypothyroidism is associated with an increased risk of CHD in those with higher TSH levels. The risk of both CHD mortality and CHD events, but not of total mortality, increases with higher concentrations of TSH and is significantly elevated in adults with TSH levels of 10 mIU/L or greater. Conversely, minimal TSH elevations are not associated with an increased risk of CHD events and CHD mortality. Our finding of no increased risk of CHD among the high proportions of adults with minimal TSH elevations is also important because many patients with minimal TSH elevations are currently treated in clinical practice. Our results might help refine a TSH threshold at which larger clinical benefits of thyroxine replacement would be expected. Our study cannot address whether these risks are attenuated or abolished by thyroxine replacement. Given the high prevalence of subclinical hypothyroidism, this question needs to be addressed in an appropriately powered randomized controlled trial.

ARTICLE INFORMATION

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Administrative, technical, or material support: Rodondi, Collet, Khaw, Newman, Gussekloo.

Study supervision: Rodondi, Westendorp, Gussekloo.

Financial Disclosures: None reported.

Funding/Support: The Cardiovascular Health Study and the research reported in this article were supported by contract numbers N01-HC-86007, N01-HC-85079 through N01-HC-85086, N01-HC-35239, N01-HC-34033, N01-HC-55222, N01-HC-75150, N01-HC-45333, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional funding from the National Institute of Neurological Disorders and Stroke. Additional support was provided through grants R01 AG-15928, R01 AG-20098, AG-027058, and AG-032317 from the National Institute on Aging, grant R01 HL-075366 from the National Heart, Lung, and Blood Institute, and grant P30-AG-024827 from the University of Pittsburgh Claude D. Pepper Older Americans Independence Center. A full list of principal investigators and institutions of the Cardiovascular Health Study can be found at http://www.chs-nhhbi.org/pi.htm. The thyroid measurements in the Cardiovascular Health Study were supported by an American Heart Association Grant-in-Aid (to Linda Fried). The Health, Aging, and Body Composition Study is supported by National Institute on Aging contract numbers N01-AG-6-2101, N01-AG-6-2102, and N01-AG-6-2106, and in part by the Intramural Research Program of the National Institutes of Health. The National Institute on Aging funded the Health Aging, and Body Composition study. The Leiden 85-plus Study was partly funded by the Dutch Ministry of Health, Welfare, and Sports. The Whickham Survey was supported by the UK Department of Health. The HUNT Study was a collaborative effort of the Faculty of Medicine, Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and the Nord-Trendelag County Council. The thyroid testing in the HUNT Study was financially supported by Wallac Oy (Turku, Finland). The Nagasaki Adult Health Study was supported by the Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan, a private, nonprofit foundation funded by the Japanese Ministry of Health, Labor and Welfare and the US Department of Energy, the latter in part through the National Academy of Sciences. This publication was supported by research protocol A-10-08 from the Radiation Effects Research Foundation. The EPIC-Norfolk study was supported by research grants from the UK Medical Research Council and the UK Cancer Research. The Brazilian Thyroid Study was supported by an unrestricted grant from the Sao Paulo State Research Foundation (Fundaçao de Amparo a’ Pesquisa do Estado de Sao Paulo grant 5077-9 to Rui Maciel). Dr Newman is supported by grant AG-023629 from the National Institute on Aging. Dr Westendorp is supported by grant NGI/NWO 911-03-016 from the National Institute on Aging and by the Netherlands Organization for Scientific Research. The majority of the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The National Institute on Aging funded the Health, Aging, and Body Composition study and reviewed the manuscript and approved its publication. The Radiation Effects Research Foundation funded the Nagasaki Adult Health Study and reviewed the manuscript and approved its publication.

Role of the Sponsor: The majority of the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The National Institute on Aging funded the Health, Aging, and Body Composition study and reviewed the manuscript and approved its publication. The Radiation Effects Research Foundation funded the Nagasaki Adult Health Study and reviewed the manuscript and approved its publication.

Statistical Evaluation: Dr Vittinghoff, professor of biostatistics, in the Department of Epidemiology and Biostatistics, University of California, San Francisco, reviewed the statistical analyses of the article.


Additional Contributions: We thank Sabrina Molinaro (Clinical Physiology Institute, Pisa, Italy) for technical help about data from the Pisa Cohort and from Rui Maciel (Escola Paulista de Medicina, Federal University of Sao Paulo, Brazil) for technical help about data from the Brazilian Thyroid Study. The persons listed in this section did not receive financial compensation.
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