Thyroid function within the reference range and fracture risk: individual participant analysis of prospective cohorts

Supplemental Data

Supplemental Table 1. Description of assays used for TSH and FT4 measurement

Study	TSH assay	TSH reference range (mIU/L)	FT4 assay	FT4 reference range pmol/L
Busselton Health Study	Immulite 2000 chemiluminescent analyzer (Diagnostic Products Corporation, Los Angeles, Calif), FS 0.02IU/L, CV 7.6%	0.4-4.0	Immulite 2000 chemiluminescent analyzer (Diagnostic Products Corporation, Los Angeles, Calif), CV 9.6%	9-23
CHS	Chemiluminescent immunometric assay (LumaTag hTSH; Nichols Institute, San Juan Capistrano, California), FS 0.008mIU/L	0.1-4.5	Direct monoclonal antibody assay (Amerlex-MAB; Amersham International, Amersham, England)	4.9-22
EPIC-Norfolk Study	AutoDelfia time resolved fluoroimmunoassay kits (Wallac, Finland), FS 0.03mIU/L, CV <3.5%	0.4-4.0	AutoDelfia time resolved fluoroimmunoassay kits (Wallac, Finland), FS 2.0pmol/L, CV <4.5%	9-20
Health ABC Study	Immunoassay (ACS; ChironDiagnosticsCorp, Emeryville,Calif), CV 4.1% at 18.94mIU/L and 3.6% at 1.26mIU/L	0.1-4.5	Competitive immunoassay (ACS; Chiron Diagnostics Corp)	10.3-23.2
HUNT Study	DELFIA hTSH Ultra (Wallac Oy, Turku, Finland), FS 0.03 mIU/L, VC 5%	0.5-3.5	DELFIA FT4, CV <7%*	8-20
InCHIANTI Study	Chemiluminescent Immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson & Johnson Medical Section, Milan, Italy), FS 0.003mIU/L, VC <5.4%	0.46-4.68	Chemiluminescent Immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson & Johnson Medical Section, Milan, Italy), FS 0.39pmol/L, CV <5.3%	9.9-28.2
Leiden 85-Plus Study	Elecsys 2010 system (Hitachi, Tokyo, Japan) with an electrochemiluminescence technique (Boehringer, Mannheim, Germany), VC 5-11%	0.3-4.8	Elecsys 2010 system (Hitachi, Tokyo, Japan) with an electrochemiluminescence technique (Boehringer, Mannheim, Germany), VC 5-8%	13-23
MrOS	ADVIA Centaur (Siemens Diagnostics, Deerfield, IL, USA)	0.55-4.78	Competitive immunoassay (Siemens Diagnostics), CV 4.1%	9.0-23.8
OPUS	Single automated analyzer using the ARCHITECT System (Abbott ARCHITECT i2000; Abbott Laboratories, Maidenhead, UK), CV<10.4%	0.13-3.48	single automated analyzer using the ARCHITECT System (Abbott ARCHITECT i2000; Abbott Laboratories, Maidenhead, UK), CV<10.4%	9.15-16.99
PROSPER	Three different immunoassays, FS 0.05 mIU/L, CV <5%	0.45-4.5	Three different immunoassays, FS 0.05 mIU/L, CV <5%	12-18**
Rotterdam Study	TSH Lumitest (Henning currently Brahms, Berlin, Germany)	0.4-4.0	Chemiluminescence assay (Vitros, ECI Immunodiagnostic System, Ortho-Clinical Diagnostics, Amersham, UK)	11-25
Sheffield Study	High-sensitivity immunoradiometric assay with reagents supplied by NETRIA (St. Bartholomew's Hospital, London, UK), CV 8.0%		One step labelled antibody assay (Amerlex MAB, Lifescreen Ltd, Watford, UK), CV 4.8%	
SOF	Chemiluminescent assay (Endocrine Science, Calabasas, California), FS 0.05mIU/L, CV<6.3%	0.5-5.5	NA	NA

Abbreviations: CHS, Cardiovascular Health Study; CV, coefficient of variation; EPIC, European Prospective Investigation of Cancer; FS, functional sensitivity; FT4, free thyroxine; Health ABC, Health, Aging and Body Composition; HUNT, Nord-Trøndelag Health; InCHIANTI, Invecchiare in Chianti; MrOS, Osteoporotic Fractures in Men Study; NA, not appropriate; OPUS, Osteoporosis and Ultrasound Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SOF, Study of Osteoporotic Fractures; TSH, thyroid-stimulating hormone.
Functional sensitivity was defined as the concentration at which the interassay CV is ≥20%.
* In the HUNT Study, FT4 was measured only if TSH was >4.0mIU/L or if the participant had known thyroid disease.
** Narrowed range among 3 different assays used for measurement.

Supplemental Table 2. Definition of fractures in each study

Study	Hip fracture	Any fracture	Non-vertebral fracture	Vertebral fracture
Busselton Health Study	ICD10: S72.0-1	Non-vertebral or vertebral fracture (first event)	Including: ICD9: 807-829. Excluding: skull/face (ICD9: 800-804)	Clinically diagnosed; cervical (ICD10: S12), thoracic (ICD10: S22) or lumbar vertebrae (ICD10: S32), vertebrae of unknown location (ICD10: T08)
CHS	ICD9: 820.0-820.9 for inpatients, plus CPT procedure code on fracture treatment for outpatients	NA	NA	NA
EPIC-Norfolk Study	ICD10: S72.0-2	Non-vertebral or vertebral fracture (first event)	Excluding skull/face, ankle, fingers, toes	Clinically diagnosed; thoracic (ICD10: S22), lumbar vertebrae (ICD10: S32), vertebrae of unknown location (ICD10: T08)
Health ABC Study	Femoral neck, intertrochanteric, proximal femur	Non-vertebral or vertebral fracture (first event)	Excluding ankle, fingers, toes	Clinically diagnosed; thoracic or lumbar vertebrae
HUNT Study	ICD9: 820.0-820.9, SIFF-95 procedure codes; ICD10: S72.0-2, S72.9, NCSP codes	NA	NA	NA
InCHIANTI Study	ICD9: 820.0-820.9 for inpatients, plus CPT procedure code on fracture treatment for outpatients	Non-vertebral or vertebral fracture (first event)	Excluding skull/face, ankle, fingers, toes	Clinically diagnosed; thoracic (ICD9: 805.2-5) or lumbar vertebrae (ICD9: 806.2-5)
Leiden 85-Plus Study	Any hip fracture	Any fracture	NA	NA
MrOS	Femoral neck, intertrochanteric, subtrochanteric	Non-vertebral or vertebral fracture (first event)	Excluding skull/face, ankle, fingers, toes	Clinically diagnosed; thoracic or lumbar vertebrae
OPUS	Any low-traumatic hip fracture	NA	Any low-traumatic non-vertebral fracture	NA
PROSPER	NA	Any fracture	NA	NA
Rotterdam Study	Any hip fracture	Non-vertebral or vertebral fracture (first event)	Excluding skull, ankle/foot, fingers/and/wrist	Any clinically diagnosed vertebral fracture
Sheffield Study	Any hip fracture	NA	Any non-vertebral fracture	NA
SOF	Any hip fracture, excluding severe traumatic fracture	Any fracture	Any non-vertebral fracture, excluding severe traumatic fracture	Any clinically diagnosed vertebral fracture, excluding severe traumatic fracture

Abbreviations: CHS, Cardiovascular Health Study; CPT; Current Procedural Terminology; EPIC, European Prospective Investigation of Cancer; GP, general practitioner; Health ABC, Health, Aging and Body Composition; HUNT, Nord-Trøndelag Health; ICD, international classification of disease; InCHIANTI, Invecchiare in Chianti; MrOS, Osteoporotic Fractures in Men Study; NA, not appropriate; OPUS, Osteoporosis and Ultrasound Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SOF, Study of Osteoporotic Fractures.

Supplemental Table 3. Study quality assessment

Study	Design	Setting	Ascertainment of exposure	Covariates available for adjustment	Assessment of fractures		Adjudication blinded to thyroid function	Median (IQR) length of follow-up	Loss to follow-up	Fractures data published[a]
					Method used	Formal adjudication				
Busselton Health Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid and anti-osteoporotic medication	ICD9 and ICD10 coded diagnoses in hospital discharge records	No	NA	20.0 (17.6-20.0)	5%	No
CHS	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-altering and anti-osteoporotic medication	Interview and hospital records reviewed by experts	No	NA	13.0 (7.6-19.0)	0%	Yes
EPIC-Norfolk Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid and thyroid-altering medication	Hospital discharge coding by data linkage with NHS central register	Yes	Yes	12.4 (11.7-13.3)	1.3%	Yes
Health ABC Study	Prospective cohort tstudy	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-alterating and anti-osteoporotic medication	Interview, hospital records and other documents reviewed by clinicians	Yes	Yes	12.7 (8.0-13.2)	<5%	Yes
HUNT Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid and thyroid-altering medication	Hospital and radiology records reviewed by physicians, health secretaries and nurses	Yes	Yes	12.2 (11.6-12.8)	<5%	Yes
InCHIANTI Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-altering and anti-osteoporotic medication	Hospital records and other documents	Yes	Yes	9.1 (7.8-9.3)	<5%	No
Leiden 85-Plus Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-alterating and anti-osteoporotic medication	Annual interview of treating GP or nursing home physician and review of their medical records	No	NA	4.8 (2.2-8.1)	<4%	Yes

Study	Design	Setting	Ascertainment of exposure	Covariates available for adjustment	Assessment of fractures		Adjudication blinded to thyroid function	Median (IQR) length of follow-up	Loss to follow-up	Fractures data published*
					Method used	Formal adjudication				
MrOS	Random sample of a prospective cohort study	Sample of community-dwelling volunteers	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-alterating and anti-osteoporotic medication	Interviewed reported fractures. Central adjudication by physician through radiology reports or X-rays	Yes	Yes	11.1 (8.1-11.8)	2%	Yes
OPUS	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-altering and anti-osteoporotic medication	Interview after 6 years follow-up, validated by medical records and imaging reviewed by radiologist	Yes	Yes	6.0 (5.8-6.3)	40%	Yes
PROSPER	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid and thyroid-altering medication	Fractures documented as adverse events	No	NA	3.3 (3.0-3.5)	<1%	No
Rotterdam Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid medication	GP and hospital registry records, reviewed by independent medical experts	Yes	Yes	15.2 (10.4-16.2)	<1%	Yes
Sheffield Study	Prospective cohort study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid medication	GP records and interviews, if confirmed by radiology or orthopedic report	Yes	Yes	10.0 (2.8-10.1)	2%	Yes
SOF	Prospective cohort study	Sample of community-dwelling volunteers	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-altering and anti-osteoporotic medication	Mail interview, with confirmation by X-rays or written report review by radiologist	Yes	Yes	14.3 (9.8-19.8)	5%	Yes

Abbreviations: BMI, body mass index; CHS, Cardiovascular Health Study; EPIC, European Prospective Investigation of Cancer; GP, general practitioner; Health ABC, Health, Aging and Body Composition; HUNT, Nord-Trøndelag Health; ICD, international classification of disease; InCHIANTI, Invecchiare in Chianti Study; IQR, interquartile range; MrOS, Osteoporotic Fractures in Men Study; OPUS, Osteoporosis and Ultrasound Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SOF, Study of Osteoporotic Fractures; TSH, thyroid-stimulating hormone.
* Four cohorts had not published their fractures data in a separate manuscript previously.

Supplemental Table 4. Analysis stratified by publication status of fractures data

	Hip fracture*		Any fracture†		Non-vertebral fracture‡		Vertebral fracture§	
Analysis by thyroid-stimulating hormone categories								
	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)
Main analysis	610/13,390	1.25 (1.05-1.49)	561/5,587	1.00 (0.83-1.19)	504/5,013	1.04 (0.85-1.26)	60/4,854	1.46 (0.82-2.61)
Studies with published fractures studies	572/12,460	1.35 (1.13-1.61)	387/4,097	1.16 (0.93-1.43)	423/4,643	1.27 (1.03-1.57)	53/3,977	1.44 (0.79-2.62)
Studies with unpublished fractures data‖	33/865	0.44 (0.21-0.90)	172/2,039	0.70 (0.50-0.96)	79/862	0.54 (0.33-0.91)	7/858	1.17 (0.14-9.88)
P-value for interaction	NA	0.0001	NA	0.17	NA	0.12	NA	0.84
Analysis by one standard deviation increase in free thyroxine¶								
	Hip fracture**		**Any fracture††**		**Non-vertebral fracture‡‡**		**Vertebral fracture§§**	
	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)
Main analysis	542/20,633	1.24 (1.12-1.37)	1,629/22,977	1.08 (1.02-1.15)	1,273/19,101	1.10 (1.03-1.18)	129/17,711	1.06 (0.86-1.30)
Studies with published fractures studies	453/17,663	1.25 (1.12-1.40)	1,003/15,192	1.09 (1.01-1.18)	1,031/16,143	1.12 (1.03-1.20)	103/14,741	1.09 (0.67-1.76)
Studies with unpublished fractures data[e]	89/2,970	1.16 (0.90-1.89)	626/7,785	1.07 (0.97-1.17)	242/2,958	1.03 (0.87-1.20)	26/2,970	1.05 (0.84-1.31)
P-value for interaction	NA	0.59	NA	0.70	NA	0.35	NA	0.89

Abbreviations: CHS, Cardiovascular Health Study; CI, confidence interval; EPIC, European Prospective Investigation of Cancer; Health ABC, Health, Aging and Body Composition; InCHIANTI, Invecchiare in Chianti; MrOS, Osteoporotic Fractures in Men Study; OPUS, Osteoporosis and Ultrasound Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SOF, Study of Osteoporotic Fractures; TSH, thyroid-stimulating hormone.FT4, free thyroxine; No., number.

All analyses were adjusted for age (as a continuous variable) and sex.

* Data on hip fractures were available for 12 studies (all but PROSPER).

† Data on any fractures were available for 9 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Leiden 85-Plus Study, PROSPER, Rotterdam Study, Busselton Health Study, SOF, Health ABC Study).

‡ Data on non-vertebral fractures were available for 9 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, Sheffield Study, OPUS, SOF, Health ABC Study).

§ Data on vertebral fracture were available for 7 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, SOF, Health ABC Study). Vertebral fracture was defined as a clinical symptomatic dorsal or lumbar fracture.

‖ Busselton Health Study, and InCHIANTI Study did not previously publish hip fracture data associated with thyroid function in a separate article.

¶ FT4was measured in all studies but SOF and Health ABC Study (FT4not measured in participants with TSH within normal range).

** Data on hip fracture were available for 10 studies with measured FT4 (all but PROSPER).

†† Data on any fracture were available for 7 studies with measured FT4 (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Leiden 85-Plus Study, PROSPER, Rotterdam Study, Busselton Health Study).

‡‡ Data on non-vertebral fracture were available for 7 studies with measured FT4 (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, Sheffield Study, OPUS).

§§ Data on vertebral fracture were available for 5 studies with measured FT4 (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study). Vertebral fracture was defined as a clinical symptomatic dorsal or lumbar fracture.

Supplemental Table 5. Risk of any, non-vertebral, and vertebral fractures according to thyroid-stimulating hormone categories

TSH level (mIU/L)	Any fracture*		Non-vertebral fracture†		Vertebral fracture‡	
	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)	No. of events/ participants	Hazard ratio (95% CI)
3.50-4.49	179/1,769	1 (Reference)	140/1,396	1 (Reference)	16/1,353	1 (Reference)
2.50-3.49	376/4,096	0.98 (0.82-1.17)	280/3,301	0.91 (0.74-1.12)	48/3,194	1.40 (0.80-2.47)
1.50-2.49	841/9,847	1.01 (0.86-1.19)	650/8,033	0.97 (0.81-1.17)	99/7,752	1.48 (0.87-2.50)
1.00-1.49	555/6,105	1.07 (0.90-1.27)	440/5,165	1.02 (0.84-1.24)	56/4,818	1.35 (0.78-2.37)
0.45-0.99	382/4,379	1.00 (0.83-1.19)	364/4,121	1.04 (0.85-1.26)	44/3,501	1.46 (0.82-2.61)
P-value for trend	NA	0.56	NA	0.19	NA	0.43

Abbreviations: CI, confidence interval; Health ABC, Health, Aging and Body Composition; No., number; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SOF, Study of Osteoporotic Fractures; TSH, thyroid-stimulating hormone.

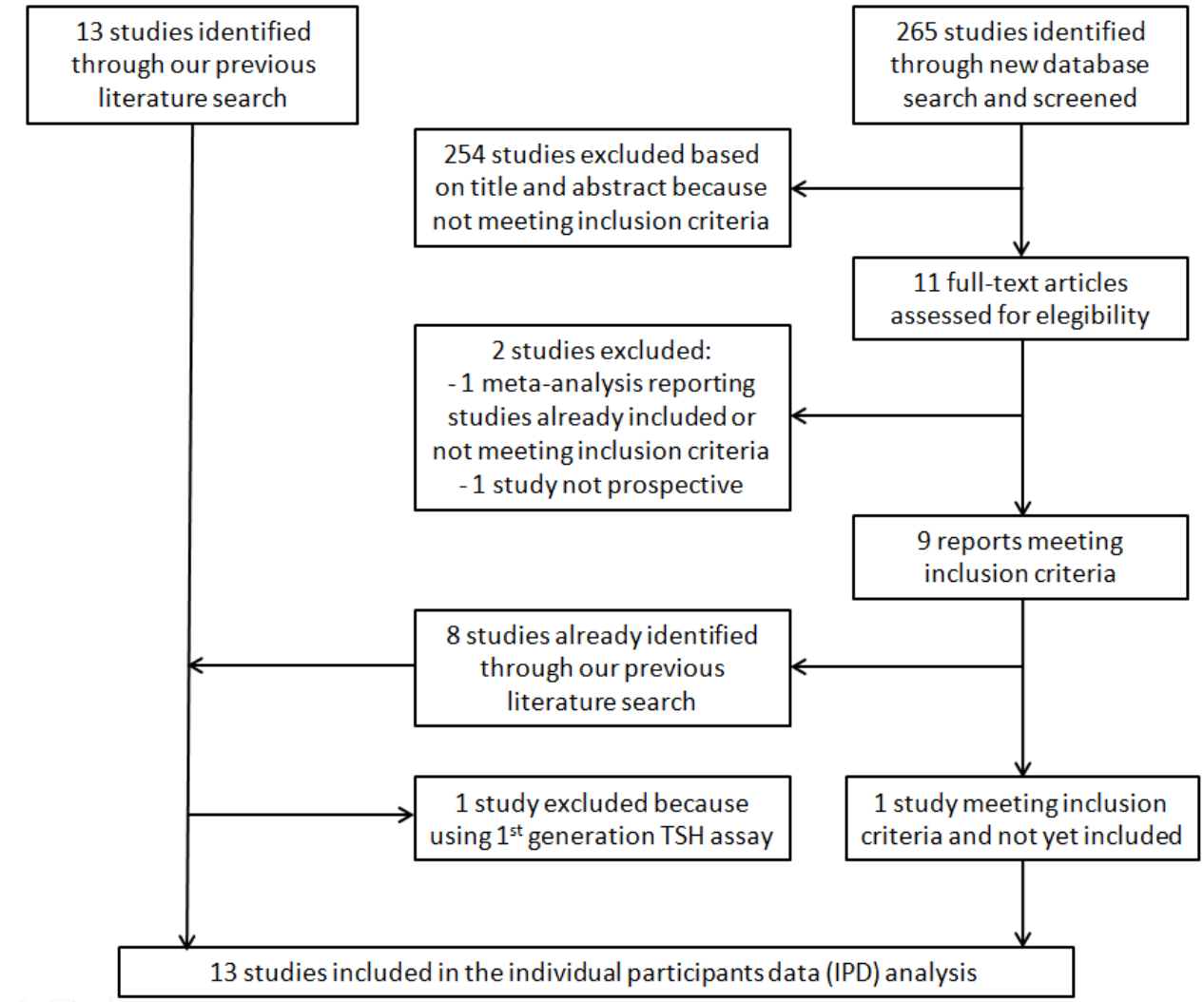
All analyses were adjusted for age (as a continuous variable) and for sex.

* Data on any fractures were available for 9 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Leiden 85-Plus Study, PROSPER, Rotterdam Study, Busselton Health Study, SOF, Health ABC Study).

† Data on non-vertebral fractures were available for 9 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, Sheffield Study, OPUS, SOF, Health ABC Study).

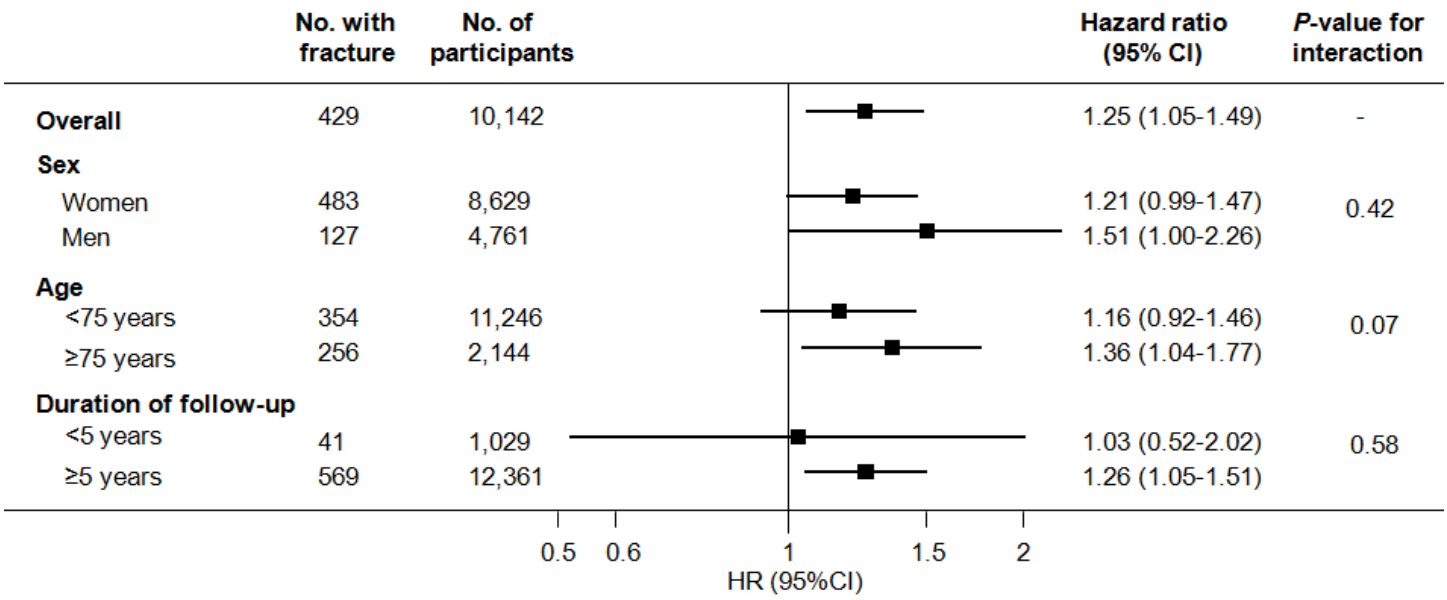
‡ Data on vertebral fractures were available for 7 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, SOF, Health ABC Study). Vertebral fracture was defined as a clinical symptomatic dorsal or lumbar fracture.

Supplemental Figure 1. Flow diagram of the studies assessed for inclusion



Abbreviations: IPD, individual participants data; TSH, thyroid-stimulating hormone.

Supplemental Figure 2. Risk of hip fracture in participants with thyroid-stimulating hormone 0.45-1.49mIU/L, compared to the reference group with thyroid-stimulating hormone 3.50-4.49mIU/L, stratified by sex, age, and duration of follow-up



Abbreviations: CI, confidence interval; HR, hazard ratio; No, number; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; TSH, thyroid-stimulating hormone.
We present a selected analysis for the TSH categories 0.45-0.99mIU/L and 3.50-4.99mIU/L. Hazard ratios are for TSH 0.45-0.99mIU/L, compared with the reference group 3.50-4.99mIU/L. The analysis stratified by sex was adjusted for age. All other analyses were adjusted for age (as a continuous variable) and sex.
Data on hip fractures were available for 12 studies (all except PROSPER).