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**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	DELFLIA hTSH Ultra (Wallac Oy, Turku, Finland), FS 0.03 mIU/L, VC 5%	0.5-3.5	DELFLIA 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, Lifescreeen 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  $\geq 20\%$ .

\* In the HUNT Study, FT4 was measured only if TSH was  $>4.0$ mIU/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 <sup>a</sup>
					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 study	Population-based study	Third generation TSH assay	Age, sex, BMI, smoking status, diabetes; thyroid, thyroid-altering 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-altering 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-altering 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**

Analysis by thyroid-stimulating hormone categories								
	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)
<b>Main analysis</b>	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)
<b>Studies with published fractures studies</b>	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)
<b>Studies with unpublished fractures data<sup>  </sup></b>	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)
<b>P-value for interaction</b>	NA	0.0001	NA	0.17	NA	0.12	NA	0.84
Analysis by one standard deviation increase in free thyroxine <sup>¶</sup>								
	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)
<b>Main analysis</b>	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)
<b>Studies with published fractures studies</b>	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)
<b>Studies with unpublished fractures data<sup>¶¶</sup></b>	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)
<b>P-value for interaction</b>	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.

¶ FT4 was measured in all studies but SOF and Health ABC Study (FT4 not 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)
<i>P</i> -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.

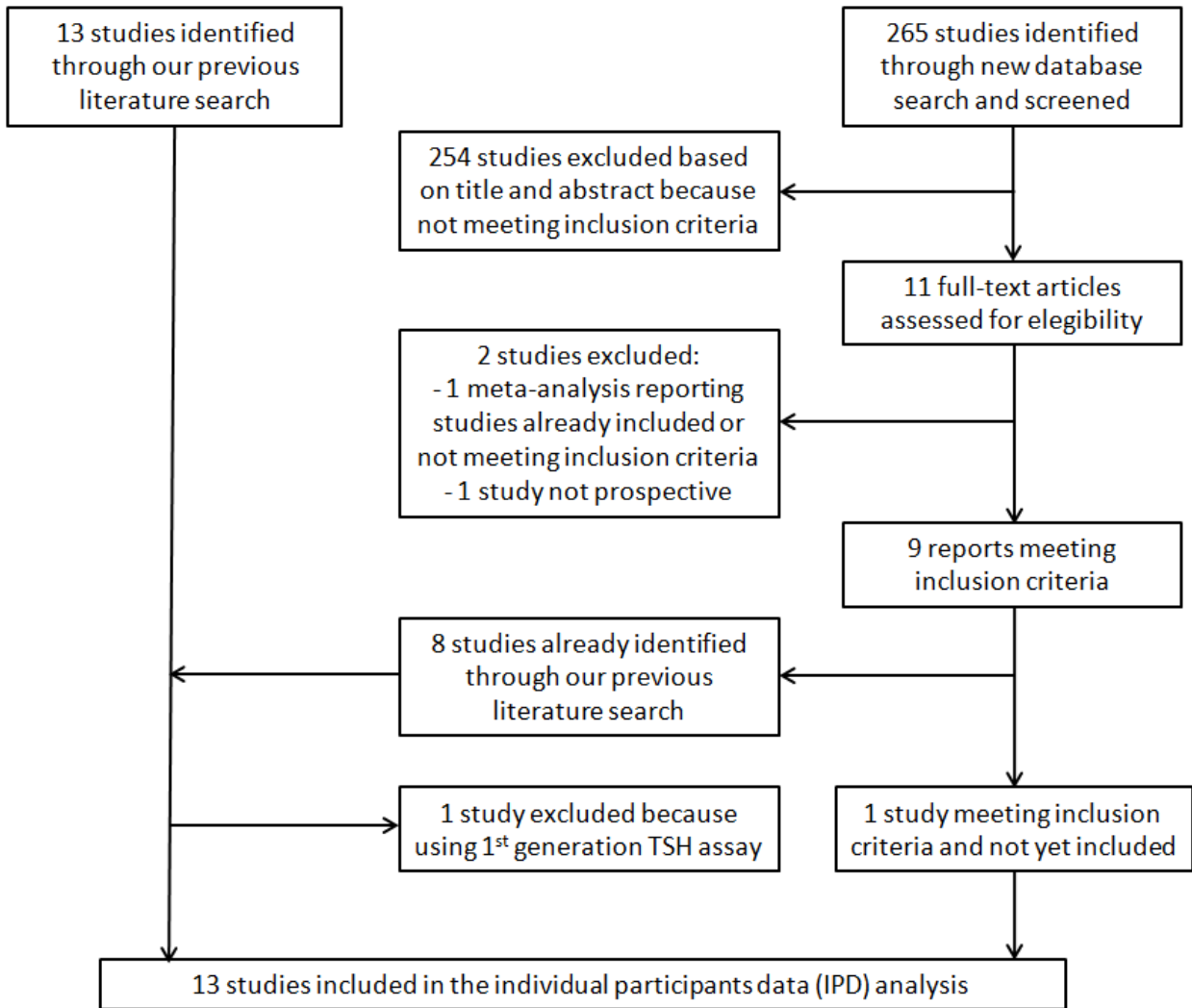
All analyses were adjusted for age (as a continuous variable) and for sex.

\* 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).

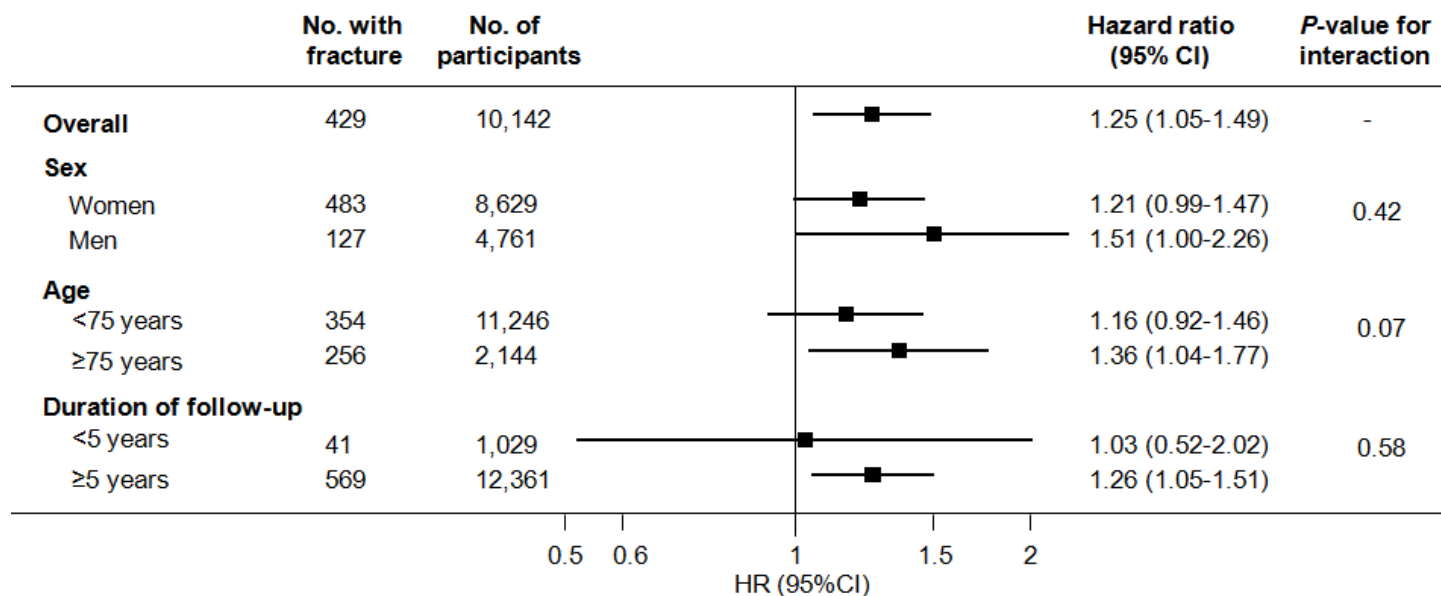
‡ Data on vertebral fractures were available for 7 studies (MrOS, EPIC-Norfolk Study, InCHIANTI Study, Rotterdam Study, Busselton Health Study, SOF, Health ABC Study). Vertebral fracture was defined as a clinical symptomatic dorsal or lumbar fracture.

**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).