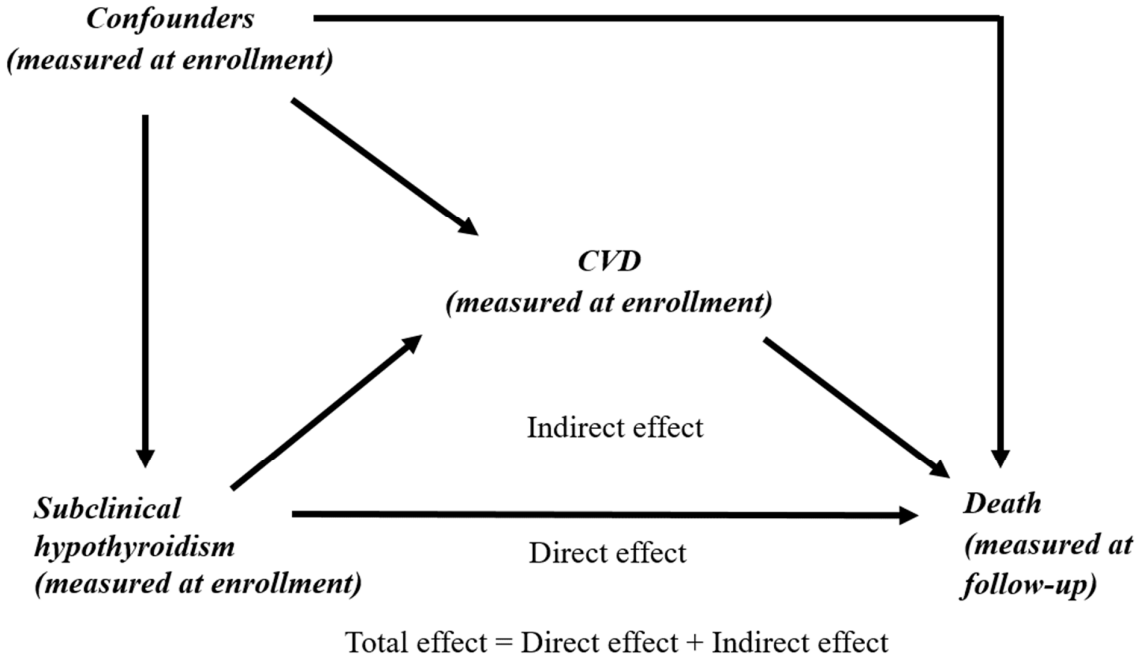
Supplementary Online Content

Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of subclinical hypothyroidism and cardiovascular disease with mortality. *JAMA Netw Open*. 2020;3(2):e1920745. doi:10.1001/jamanetworkopen.2019.20745

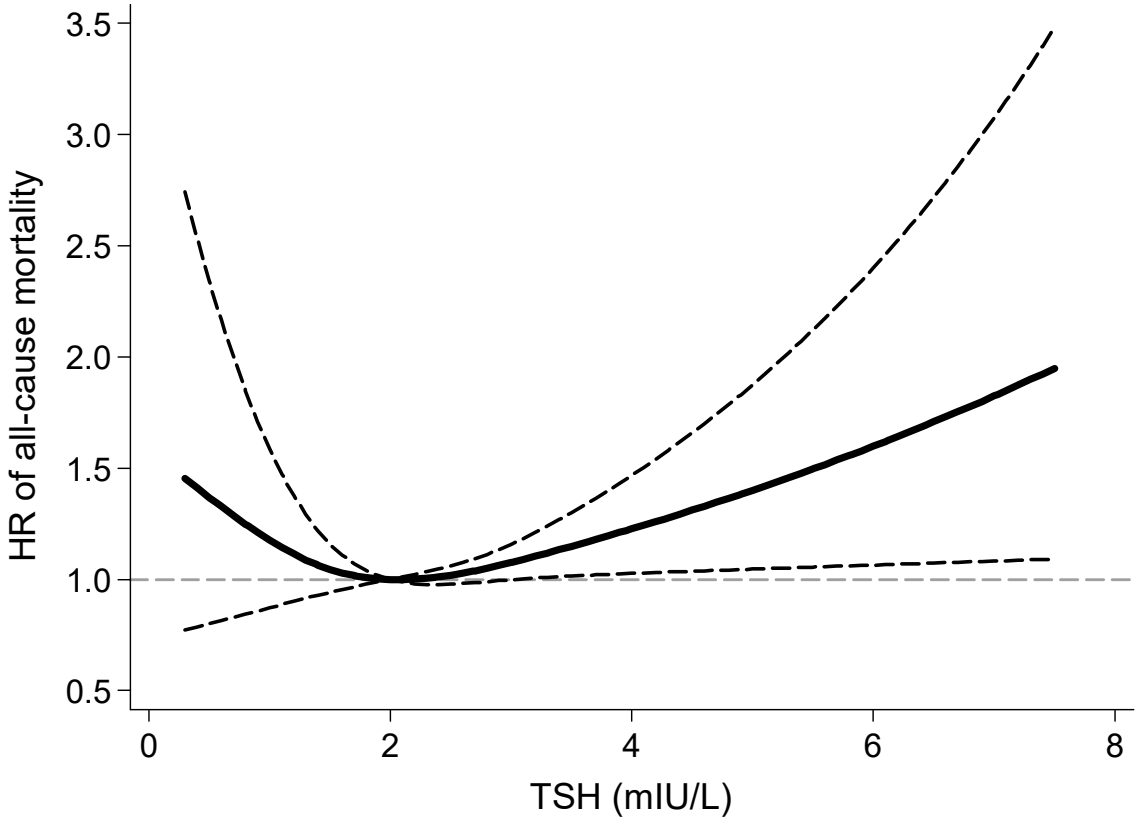
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Causal diagram under investigation



Confounders in our main Model (Model 2): age, sex, race/ethnicity, education status, smoking, previous cancer history, and eGFR. We also adjusted for diabetes, hypertension, statin prescription, and BMI in addition to covariates in Model 2 in the sensitivity analysis.

eFigure 2. Association between serum TSH concentrations and all-cause mortality additionally adjusted for comorbidities using a restricted cubic spline regression model in NHANES 2001-2002 and 2007-2012 followed through 2015.



Adjusted for age, sex, race/ethnicity, education status, smoking, previous cancer history, eGFR, diabetes, hypertension, statin prescription, and BMI. Restricted cubic spline regression model was conducted with three knots at 10th, 50th, and 90th percentile of TSH (mIU/L). The dashed lines represent the 95% CIs for the spline model (reference is 2.0 mIU/L). The range of TSH was restricted to 0.34–7.5 mIU/L because predictions >7.5 mIU/L (95th percentile) are based on too few data point

eTable 1. Associations between serum TSH concentrations and all-cause mortality additionally adjusted for comorbidities in NHANES 2001-2002 and 2007-2012 followed through 2015.

All-cause mortality	Event N/ Total N	Adjusted HR (95% CI) [a]
Low-normal TSH	107/2865	1.30 (0.92-1.84)
Middle-normal TSH	105/2836	Ref
High-normal TSH	145/2818	1.20 (0.90-1.61)
Subclinical hypothyroidism	18/160	1.80 (1.02-3.19)

[a] HR adjusted for age, sex, race/ethnicity, education status, smoking, previous cancer history, eGFR, diabetes, hypertension, statin prescription, and BMI. The results did not change when we additionally adjusted for systolic blood pressure, HbA1c, cholesterol levels, antihypertensive medication use, and antidiabetic medication use.

eTable 2. Direct and indirect Associations (hazard ratio scale [95%CI]) of serum TSH concentrations on all-cause mortality through cardiovascular disease additionally adjusted for comorbidities in NHANES 2001-2002 and NHANES 2007-2012 followed through 2015. [a,b]

	Event N/ Total N	Total effect (TE)	Direct effect (DE)	Indirect effect (IE)	%mediated [c]
Low-normal TSH	107/2865	1.28 (0.86-1.92)	1.27 (0.95-1.65)	1.00 (0.76-1.35)	1.7%
Middle-normal TSH	105/2836	Ref	Ref	Ref	Ref
High-normal TSH	145/2818	1.22 (0.97-1.59)	1.20 (0.96-1.57)	1.01 (1.00-1.04)	5.8%
Subclinical hypothyroidism	18/160	1.84 (1.13-2.75)	1.61 (0.92-2.58)	1.15 (0.97-1.59)	23.1%

[a] HR adjusted for age, sex, race/ethnicity, education status, smoking, previous cancer history, eGFR, diabetes, hypertension, statin prescription, and BMI.

[b] 1000 iterations were performed for bootstrapping to estimate 95% bias-corrected confidence interval.

[c] %mediated was calculated by log(IE)/log(TE).

eTable 3. Direct and indirect Associations (hazard ratio scale [95%CI]) of serum TSH concentrations on all-cause mortality through cardiovascular disease using different cut-off for TSH (0.4-4.3 mIU/L as normal range) in NHANES 2001-2002 and NHANES 2007-2012 followed through 2015 [a,b]

	Event N/ Total N	Total effect (TE)	Direct effect (DE)	Indirect effect (IE)	%mediated [c]
Low-normal TSH	118/2854	1.34 (0.89-1.96)	1.32 (1.02-1.70)	1.02 (0.76-1.34)	5.8%
Middle-normal TSH	113/2856	Ref	Ref	Ref	Ref
High-normal TSH	166/2851	1.43 (1.15-1.84)	1.41 (1.11-1.78)	1.02 (1.00-1.05)	5.2%
Subclinical hypothyroidism	35/354	1.36 (0.91-1.90)	1.33 (0.88-1.85)	1.02 (0.93-1.13)	5.6%

Low-normal, 0.40–1.19 mIU/L; middle-normal, 1.20–1.91 mIU/L; and high-normal, 1.92–4.30 mIU/L.

[a] HR adjusted for age, sex, race/ethnicity, education status, smoking, previous cancer history, and eGFR.

[b] 1000 iterations were performed for bootstrapping to estimate 95% bias-corrected confidence interval.

[c] %mediated was calculated by log(IE)/log(TE).

eTable 4. Direct and indirect Associations (hazard ratio scale [95%CI]) of serum TSH concentrations on all-cause mortality through cardiovascular disease stratified by age in NHANES 2001-2002 and 2007-2012 followed through 2015. [a,b]

Age ≥60	Event N/ Total N	Total effect (TE)	Direct effect (DE)	Indirect effect (IE)	%mediated [c]
Low-normal TSH	110/970	1.16 (0.79-1.72)	1.15 (0.87-1.47)	1.01 (0.76-1.32)	4.6%
Middle-normal TSH	95/969	Ref	Ref	Ref	Ref
High normal TSH	120/969	1.31 (1.03-1.70)	1.29 (1.01-1.68)	1.02 (1.00-1.05)	6.0%
Subclinical hypothyroidism	21/82	2.15 (1.35-3.35)	1.92 (1.09-2.84)	1.12 (0.94-1.44)	14.8%
Age <60	Event N/ Total N	Total effect (TE)	Direct effect (DE)	Indirect effect (IE)	%mediated [c]
Low-normal TSH	32/1996	1.56 (0.72-3.26)	1.56 (0.91-2.71)	1.00 (0.54-1.67)	0.0%
Middle-normal TSH	25/1970	Ref	Ref	Ref	Ref
High normal TSH	32/1981	1.56 (0.99-2.61)	1.58 (1.01-2.61)	0.99 (0.89-1.04)	-3.1%
Subclinical hypothyroidism	0/80	NA [d]			

Age ≥60: Low-normal, 0.34–1.34 mIU/L; middle-normal, 1.35–2.17 mIU/L; and high-normal, 2.18–5.60 mIU/L.

Age <60: Low-normal, 0.34–1.15 mIU/L; middle-normal, 1.16–1.84 mIU/L; and high-normal, 1.85–5.60 mIU/L.

[a] Adjusted for age, sex, race/ethnicity, education status, smoking, previous cancer history, and eGFR.

[b] 1000 iterations were performed for bootstrapping to estimate 95% bias-corrected confidence interval.

[c] %mediated was calculated by log(IE)/log(TE).

[d] The effect could not be calculated due to sparse data.