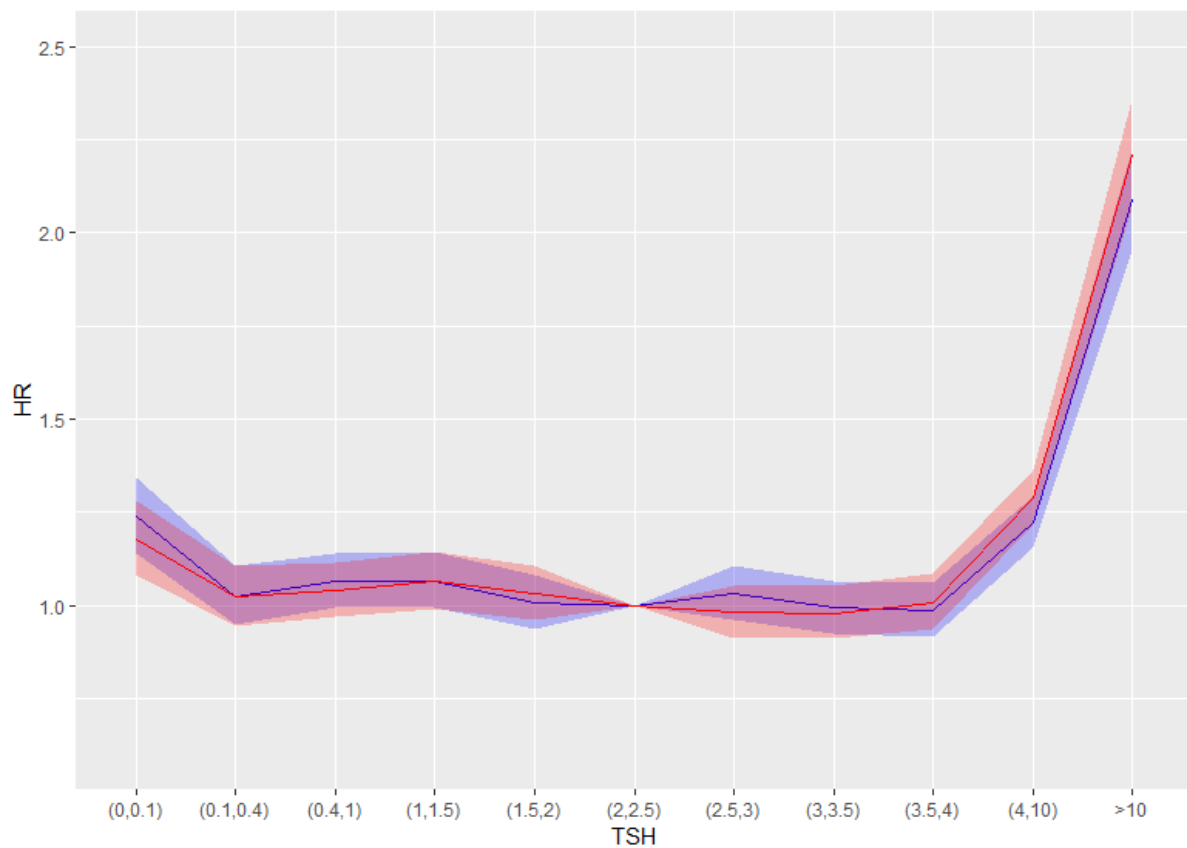# Supplementary methods 1: Multiple imputation of missing TSH values

In the primary analysis, missing TSH values were imputed using last observation carried forward. In a sensitivity analysis for the mortality outcome, multiple imputation was used to impute missing TSH values; covariates used in the imputation were sex, age, BMI, Townsend deprivation quintile, smoking status, diabetes, hypertension, and levothyroxine prescription. This did not significantly impact on the results, as illustrated in Supplementary Figure 1 below.

Supplementary figure 1. All-cause mortality hazard ratio for TSH category relative to the 2-2.5 mIU/L reference category using last observation carried forward (red) and multiple imputation (blue) to impute missing TSH values.

Supplementary methods 2: Extended Cox proportional hazards model description

Time-independent variables use participants' baseline measures. We treated yearly TSH measurements as a time-dependent predictor[1,2] for each outcome. Each yearly TSH for an individual patient appears as a separate observation in the extended Cox proportional hazards model. The Cox proportional hazards model may be written as follows:

$$h_i(t) = h_0(t) \exp(\sum_{j=1}^{p} x_{ij}(t)\beta_j)$$

where h_0 is the baseline hazard rate when all covariates are equal to zero, $x_{ij}(t)$ is the jth covariate of the ith individual that may be either time-varying or time fixed over the time interval t (in our case t stands for year), and β is a 1 x p vector of regression coefficients.

[1] Fisher, L. D. and D. Y. Lin (1999). "Time-dependent covariates in the Cox proportional-hazards regression model." Annual review of public health 20(1): 145-157.
[2] Therneau, T., et al. (2013). "Using time dependent covariates and time dependent coefficients in the cox model." Red 2: 1.

Supplementary Table A. Length of follow-up

Outcomes	Length of follow-up				Total Population
	1-5 years	6-10 years	11-15 years	≥16 years	
IHD	69,641	45,341	25,500	4,679	145,161
HF	73,330	48,788	27,951	5,141	155,210
Stroke/TIA	72,993	47,726	26,999	4,906	152,624
AF	72,107	47,626	27,006	4,912	151,651
All Fractures	63,530	40,300	22,105	3,843	129,778
Fragility Fracture	70,676	45,979	25,578	4,542	146,775
Death	75,949	50,304	28,875	5,311	160,439

Supplementary Table B. Adjusted, sex stratified and age stratified hazard ratios (HR) for ischaemic heart disease for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	1.064 (0.894 to 1.267)	0.49	0.929 (0.664 to 1.301)	1.124 (0.916 to 1.379)	1.119 (0.876 to 1.431)	0.952 (0.741 to 1.225)
0.1 – 0.4	1.005 (0.852 to 1.184)	0.96	1.129 (0.839 to 1.517)	0.959 (0.787 to 1.168)	1.012 (0.794 to 1.289)	1.008 (0.806 to 1.261)
0.4 – 1.0	1.093 (0.948 to 1.261)	0.22	1.098 (0.844 to 1.428)	1.092 (0.921 to 1.294)	1.136 (0.921 to 1.402)	1.062 (0.874 to 1.291)
1.0 – 1.5	1.048 (0.901 to 1.219)	0.54	1.057 (0.803 to 1.391)	1.043 (0.870 to 1.251)	1.012 (0.807 to 1.269)	1.078 (0.879 to 1.320)
1.5 – 2.0	1.068 (0.920 to 1.240)	0.38	0.940 (0.711 to 1.243)	1.128 (0.945 to 1.346)	1.204 (0.968 to 1.497)	0.955 (0.777 to 1.174)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.985 (0.847 to 1.145)	0.84	0.932 (0.709 to 1.224)	1.012 (0.844 to 1.212)	1.039 (0.827 to 1.305)	0.957 (0.783 to 1.170)
3.0 – 3.5	1.005 (0.864 to 1.169)	0.95	1.005 (0.769 to 1.314)	1.006 (0.837 to 1.208)	1.034 (0.819 to 1.303)	0.999 (0.818 to 1.219)
3.5 – 4.0	0.912 (0.779 to 1.069)	0.26	0.823 (0.619 to 1.093)	0.962 (0.794 to 1.164)	1.004 (0.789 to 1.277)	0.864 (0.699 to 1.067)
4.0 – 10	0.938 (0.829 to 1.061)	0.31	0.881 (0.709 to 1.096)	0.972 (0.837 to 1.128)	1.001 (0.830 to 1.206)	0.924 (0.785 to 1.088)
>10	1.182 (1.015 to 1.376)	0.03	1.261 (0.979 to 1.622)	1.082 (0.891 to 1.316)	1.258 (1.003 to 1.579)	1.118 (0.911 to 1.372)

Supplementary Table C. Adjusted, sex stratified and age stratified hazard ratios (HR) for heart failure for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	0.793 (0.636 to 0.988)	0.04	0.653 (0.419 to 1.016)	0.848 (0.657 to 1.094)	0.776 (0.507 to 1.190)	0.737 (0.569 to 0.954)
0.1 – 0.4	0.757 (0.621 to 0.923)	0.006	0.949 (0.671 to 1.342)	0.686 (0.539 to 0.873)	0.676 (0.445 to 1.028)	0.762 (0.608 to 0.954)
0.4 – 1.0	0.912 (0.775 to 1.072)	0.26	0.911 (0.675 to 1.230)	0.909 (0.749 to 1.103)	0.832 (0.589 to 1.175)	0.925 (0.769 to 1.111)
1.0 – 1.5	0.961 (0.812 to 1.136)	0.64	0.936 (0.688 to 1.273)	0.965 (0.790 to 1.179)	0.823 (0.571 to 1.187)	0.996 (0.825 to 1.203)
1.5 – 2.0	0.929 (0.787 to 1.098)	0.39	1.006 (0.751 to 1.347)	0.896 (0.732 to 1.096)	0.980 (0.690 to 1.392)	0.912 (0.755 to 1.101)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.849 (0.718 to 1.004)	0.06	0.818 (0.607 to 1.102)	0.866 (0.708 to 1.059)	1.148 (0.813 to 1.619)	0.782 (0.645 to 0.947)
3.0 – 3.5	0.971 (0.825 to 1.142)	0.72	0.964 (0.726 to 1.281)	0.972 (0.797 to 1.186)	1.205 (0.853 to 1.703)	0.935 (0.778 to 1.124)
3.5 – 4.0	0.888 (0.749 to 1.053)	0.17	0.999 (0.752 to 1.327)	0.825 (0.665 to 1.022)	0.882 (0.596 to 1.304)	0.904 (0.748 to 1.092)
4.0 – 10	1.091 (0.958 to 1.242)	0.19	1.122 (0.896 to 1.406)	1.077 (0.918 to 1.262)	1.025 (0.766 to 1.372)	1.171 (1.013 to 1.353)
>10	1.419 (1.208 to 1.669)	<0.001	1.523 (1.164 to 1.994)	1.352 (1.103 to 1.657)	1.602 (1.126 to 2.278)	1.492 (1.244 to 1.788)

Supplementary Table D. Adjusted, sex stratified and age stratified hazard ratios (HR) for stroke/TIA for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	1.116 (0.956 to 1.302)	0.16	1.286 (0.930 to 1.778)	1.071 (0.898 to 1.276)	1.318 (1.030 to 1.685)	0.902 (0.736 to 1.105)
0.1 – 0.4	0.913 (0.787 to 1.060)	0.23	1.039 (0.757 to 1.427)	0.880 (0.743 to 1.042)	0.944 (0.729 to 1.222)	0.884 (0.736 to 1.062)
0.4 – 1.0	0.973 (0.855 to 1.107)	0.68	1.088 (0.828 to 1.430)	0.942 (0.813 to 1.090)	0.837 (0.661 to 1.059)	1.035 (0.887 to 1.207)
1.0 – 1.5	0.978 (0.854 to 1.121)	0.75	1.007 (0755 to 1.344)	0.966 (0.829 to 1.127)	0.896 (0.702 to 1.146)	1.008 (0.857 to 1.187)
1.5 – 2.0	0.962 (0.841 to 1.102)	0.58	1.056 (0.799 to 1.397)	0.935 (0.801 to 1.091)	1.009 (0.794 to 1.282)	0.929 (0.789 to 1.095)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.979 (0.858 to 1.119)	0.76	1.126 (0.861 to 1.474)	0.935 (0.802 to 1.089)	1 011(0.792 to 1.292)	0.969 (0.827 to 1.136)
3.0 – 3.5	0.863 (0.751 to 0.992)	0.04	0.991 (0.751 to 1.308)	0.822 (0.699 to 0.966)	0.865 (0.666 to 1.123)	0.874 (0.742 to 1.031)
3.5 – 4.0	0.869 (0.754 to 1.002)	0.05	0.991 (0.749 to 1.309)	0.830 (0.703 to 0.981)	0.988 (0.761 to 1.283)	0.836 (0.706 to 0.992)
4.0 – 10	0.896 (0.803 to 0.999)	0.05	0.959 (0.768 to 1.198)	0.878 (0.774 to 0.996)	0.906 (0.739 to 1.112)	0.927 (0.814 to 1.055)
>10	1.001 (0.866 to 1.156)	0.99	1.029 (0.779 to 1.359)	0.997 (0.841 to 1.182)	1.149 (0.887 to 1.490)	0.987 (0.829 to 1.174)

Supplementary Table E. Adjusted, sex stratified and age stratified hazard ratios (HR) for atrial fibrillation for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	0.998 (0.851 to 1.169)	0.98	0.979 (0.719 to 1.334)	0.830 (0.689 to 0.999)	0.999 (0.756 to 1.321)	0.906 (0.746 to 1.102)
0.1 – 0.4	0.859 (0.740 to 0.998)	0.05	0.929 (0.696 to 1.242)	0.792 (0.665 to 0.943)	0.638 (0.471 to 0.864)	0.932 (0.785 to 1.107)
0.4 – 1.0	0.952 (0.838 to 1.081)	0.45	0.942 (0.734 to 1.209)	0.890 (0.768 to 1.032)	0.934 (0.734 to 1.188)	0.936 (0.805 to 1.088)
1.0 – 1.5	0.951 (0.832 to 1.088)	0.47	0.936 (0.720 to 1.215)	0.893 (0.763 to 1.044)	0.978 (0.759 to 1.258)	0.920 (0.785 to 1.079)
1.5 – 2.0	1.006 (0.883 to 1.146)	0.93	0.980 (0.761 to 1.263)	0.978 (0.840 to 1.139)	1.174 (0.921 to 1.497)	0.927 (0.794 to 1.082)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.951 (0.834 to 1.084)	0.45	1.039 (0.813 to 1.327)	0.940 (0.805 to 1.097)	0.930 (0.715 to 1.211)	0.961 (0.827 to 1.117)
3.0 – 3.5	0.918 (0.804 to 1.049)	0.21	1.041 (0.815 to 1.329)	0.913 (0.779 to 1.071)	0.881 (0.669 to 1.159)	0.945 (0.811 to 1.100)
3.5 – 4.0	1.093 (0.959 to 1.246)	0.18	1.111 (0.871 to 1.416)	1.153 (0.987 to 1.348)	0.919 (0.692 to 1.222)	1.161 (1.001 to 1.346)
4.0 – 10	0.967 (0.869 to 1.075)	0.53	1.016 (0.833 to 1.239)	1.070 (0.944 to 1.214)	0.934 (0.752 to 1.161)	1.032 (0.913 to 1.166)
>10	1.038 (0.897 to 1.199)	0.62	0.988 (0.765 to 1.276)	1.137 (0.953 to 1.357)	0.904 (0.661 to 1.237)	1.152 (0.977 to 1.357)

Supplementary Table F. Adjusted, sex stratified and age stratified hazard ratios (HR) for mortality for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	1.177 (1.081 to 1.281)	<0.001	1.192 (1.021 to 1.391)	1.186 (1.071 to 1.313)	1.115 (0.922 to 1.349)	1.079 (0.981 to 1.187)
0.1 – 0.4	1.021 (0.943 to 1.105)	0.61	0.990 (0.854 to 1.148)	1.041 (0.947 to 1.145)	1.064 (0.886 to 1.279)	0.970 (0.888 to 1.059)
0.4 – 1.0	1.039 (0.970 to 1.114)	0.27	1.007 (0.887 to 1.142)	1.059 (0.974 to 1.151)	1.061 (0.900 to 1.250)	0.998 (0.924 to 1.077)
1.0 – 1.5	1.064 (0.991 to 1.144)	0.09	1.028 (0.903 to 1.169)	1.082 (0.992 to 1.179)	1.039 (0.873 to 1.236)	1.046 (0.967 to 1.132)
1.5 – 2.0	1.030 (0.959 to 1.107)	0.41	0.958 (0.844 to 1.089)	1.066 (0.978 to 1.162)	1.179 (0.995 to 1.396)	0.991 (0.916 to 1.072)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.981 (0.913 to 1.053)	0.59	0.937 (0.827 to 1.062)	1.001 (0.917 to 1.092)	1.023 (0.855 to 1.225)	0.978 (0.904 to 1.057)
3.0 – 3.5	0.978 (0.910 to 1.052)	0.55	0.876 (0.772 to 0.996)	1.028 (0.942 to 1.123)	0.996 (0.828 to 1.199)	0.988 (0.913 to 1.068)
3.5 – 4.0	1.007 (0.935 to 1.084)	0.86	0.939 (0.828 to 1.066)	1.041 (0.950 to 1.139)	1.013 (0.836 to 1.227)	1.029 (0.949 to 1.114)
4.0 – 10	1.289 (1.218 to 1.364)	<0.001	1.202 (1.091 to 1.324)	1.333 (1.244 to 1.429)	1.393 (1.208 to 1.606)	1.369 (1.288 to 1.456)
>10	2.207 (2.067 to 2.356)	<0.001	1.984 (1.775 to 2.217)	2.319 (2.138 to 2.515)	2.632 (2.242 to 3.090)	2.331 (2.169 to 2.504)

Supplementary Table G. Adjusted, sex stratified and age stratified hazard ratios (HR) for all fractures for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	0.991 (0.889 to 1.106)	0.88	1.013 (0.728 to 1.411)	0.988 (0.880 to 1.109)	0.981 (0.849 to 1.133)	0.959 (0.810 to 1.136)
0.1 – 0.4	0.948 (0.855 to 1.051)	0.31	1.106 (0.818 to 1.494)	0.928 (0.832 to 1.036)	0.985 (0.857 to 1.131)	0.908 (0.778 to 1.060)
0.4 – 1.0	0.971 (0.887 to 1.064)	0.53	1.223 (0.944 to 1.585)	0.939 (0.853 to 1.036)	0.992 (0.876 to 1.123)	0.942 (0.824 to 1.077)
1.0 – 1.5	1.016 (0.924 to 1.118)	0.74	1.113 (0.845 to 1.466)	1.002 (0.906 to 1.109)	1.061 (0.932 to 1.207)	0.945 (0.819 to 1.089)
1.5 – 2.0	1.014 (0.922 to 1.114)	0.78	1.125 (0.859 to 1.474)	0.999(0.903 to 1.105)	1.079 (0.948 to 1.228)	0.929 (0.808 to 1.068)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	1.014 (0.921 to 1.115)	0.78	0.915 (0.692 to 1.210)	1.029 (0.929 to 1.139)	1.065 (0.933 to 1.216)	0.966 (0.843 to 1.107)
3.0 – 3.5	0.958 (0.869 to 1.057)	0.40	1.059 (0.809 to 1.386)	0.945 (0.851 to 1.051)	0.928 (0.806 to 1.068)	1.002 (0.873 to 1.149)
3.5 – 4.0	0.999 (0.904 to 1.105)	0.99	0.939 (0.709 to 1.244)	1.014 (0.911 to 1.129)	0.934 (0.807 to 1.080)	1.072 (0.933 to 1.232)
4.0 – 10	1.028 (0.950 to 1.111)	0.50	1.178 (0.949 to 1.462)	1.005 (0.924 to 1.093)	0.961 (0.859 to 1.075)	1.103 (0.988 to 1.232)
>10	1.052 (0.945 to 1.172)	0.35	1.252 (0.961 to 1.632)	1.007 (0.894 to 1.134)	0.863 (0.738 to 1.008)	1.226 (1.057 to 1.423)

Supplementary Table H. Adjusted, sex stratified and age stratified hazard ratios (HR) for fragility fractures for each thyroid stimulating hormone (TSH) category relative to the reference category (2-2.5 mIU/L)

TSH Category (mIU/L)	Adjusted Model HR (95% CI)	p-value	Sex Stratified Male HR (95% CI)	Female HR (95% CI)	Age Stratified Age ≤ 65 HR (95% CI)	Age >65 HR (95% CI)
< 0.1	1.067 (0.938 to 1.215)	0.32	1.016 (0.681 to 1.515)	1.074 (0.936 to 1.232)	1.034 (0.858 to 1.246)	0.997 (0.830 to 1.197)
0.1 – 0.4	0.937 (0.828 to 1.060)	0.30	0.911 (0.623 to 1.331)	0.939 (0.824 to 1.071)	0.924 (0.768 to 1.112)	0.928 (0.785 to 1.097)
0.4 – 1.0	0.973 (0.873 to 1.085)	0.62	1.091 (0.797 to 1.493)	0.959 (0.854 to 1.076)	0.966 (0.820 to 1.138)	0.956 (0.826 to 1.106)
1.0 – 1.5	0.961 (0.856 to 1.078)	0.50	0.989 (0.707 to 1.382)	0.957 (0.846 to 1.082)	0.953 (0.801 to 1.134)	0.944 (0.809 to 1.102)
1.5 – 2.0	0.942 (0.839 to 1.056)	0.31	0.985 (0.709 to 1.368)	0.935 (0.827 to 1.057)	0.903 (0.756 to 1.078)	0.963 (0.828 to 1.119)
2.0 – 2.5	1	-	1	-	1	-
2.5 – 3.0	0.968 (0.864 to 1.086)	0.58	0.969 (0.702 to 1.339)	0.969 (0.857 to 1.095)	0.844 (0.701 to 1.017)	1.063 (0.919 to 1.230)
3.0 – 3.5	0.915 (0.813 to 1.030)	0.14	0.849 (0.607 to 1.186)	0.926 (0.816 to 1.051)	0.819 (0.676 to 0.994)	0.999 (0.859 to 1.162)
3.5 – 4.0	0.962 (0.853 to 1.086)	0.53	0.860 (0.614 to 1.206)	0.982 (0.863 to 1.118)	0.835 (0.684 to 1.021)	1.064 (0.913 to 1.239)
4.0 – 10	1.026 (0.934 to 1.126)	0.59	1.125 (0.871 to 1.452)	1.006 (0.909 to 1.113)	0.955 (0.823 to 1.108)	1.112 (0.985 to 1.254)
>10	1.150 (1.013 to 1.306)	0.03	1.027 (0.739 to 1.427)	1.176 (1.024 to 1.349)	0.854 (0.689 to 1.058)	1.371 (1.169 to 1.607)