Systematic Review

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Subclinical hyperthyroidism and the risk of developing cardiovascular disease – a systematic review

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ABSTRACT

INTRODUCTION: It is debated whether the presence of subclinical hyperthyroidism (SH) constitutes an increased risk of cardiovascular disease. This review presents a summary of the literature examining the association between SH and atrial fibrillation (AF), heart failure (HF), myocardial infarction (MI) and cardiovascular mortality.

METHODS: A systematic literature search of the PubMed database was performed. Studies were included if they were of observational design, about SH in humans, and had AF, HF, MI and/or cardiovascular mortality as outcome, were published in either Danish or English language and included euthyroid controls.

RESULTS: A total of 33 papers were suitable for inclusion. Thus, 13 papers on AF and five papers on HF were included for review and supported an association between SH and AF and HF, respectively. In all, 14 papers on MI and 15 papers on cardiovascular mortality were included for review; but, overall, they did not support an association between SH and MI or cardiovascular mortality.

CONCLUSIONS: Based on our review, current literature supports an association between SH and AF and HF, respectively; but not between SH and MI or cardiovascular mortality.

KEY POINTS

- Subclinical hyperthyroidism is associated with atrial fibrillation and congestive heart failure.
- Subclinical hyperthyroidism does not seem to be associated with myocardial infarction or cardiovascular mortality.
- Intervention studies investigating whether or not treatment of subclinical hyperthyroidism reduces the risk of cardiovascular disease are lacking.

The prevalence of subclinical hyperthyroidism (SH) is around 1% in iodine-replete areas and around 10% in iodine-deficient areas [1]. SH is diagnosed according to biochemical criteria, i.e. a low level of thyroid-stimulating hormone (TSH) and normal levels of circulating peripheral hormones (free thyroxin (T4) and triiodothyronine and/or free triiodothyronine (T3)) [2].

According to clinical guidelines, antithyroid treatment should be considered if TSH level is < 0.1 mIU/l or if TSH level is between 0.1 mIU/l and the lower limit of the reference range at repetitive measurements and the patient has hyperthyroid symptoms [2]. It is well-known that SH increases the risk of atrial fibrillation (AF) [1] and osteoporosis, [1] but it remains unclear if SH also increases the risk of cardiovascular diseases (CVDs) in general.

A number of potential pathophysiological links between endogenous SH and CVD have been described. Overt hyperthyroidism affects the cardiac pacemaker cells resulting in increased chronotropic and inotropic effects. In patients with SH, a higher 24-hour heart rate and an increased number of ventricular and supraventricular extrasystoles have been reported as well as increased ventricular mass and impaired left ventricular performance. Increased carotid intima-media thickness has also been reported in SH patients, and there is an association between increased carotid intima-media thickness and atherosclerotic cardiovascular events, suggesting an increased cardiovascular morbidity and mortality in SH [2, 3]. A small study of SH caused by levothyroxine treatment showed improvement in myocardial structure when tailoring the dose of levothyroxine from TSH level < 0.1 mIU/l to TSH suppression > 0.1 mIU/l, suggesting possible reversibility in cardiac changes in patients with SH – at least in exogenous SH [4].

Through a systematic literature search, this systematic review explored whether or not there is an association between SH and the risk of developing AF, myocardial infarction (MI), heart failure (HF) and CVD mortality.

METHODS

A systematic literature search with the search terms ("thyroid dysfunction" OR "subclinical thyroid dysfunction" OR "thyrotoxicosis" OR "subclinical thyrotoxicosis" OR "hyperthyroidism" OR "subclinical hyperthyroidism") AND ("atrial fibrillation" OR "heart failure" OR "myocardial infarction" OR "cardiovascular mortality" OR "cardiovascular disease") was performed in PubMed on 12 March 2020. Included were studies of observational design, about SH in humans, with AF, HF, MI and/or CVD mortality as outcome that were published in either Danish or English language. The search was performed by SBS. When in doubt if a paper should be included, the other authors were consulted for their opinion. The Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess the risk of bias [5]. For cross-sectional studies, a modified version of the NOS was used (https://ugeskriftet.dk/files/a12190701_supplementary.pdf). This systematic review was reported according to the PRISMA guidelines [6].

RESULTS

The literature search returned 2,145 records (**Figure 1**, https://ugeskriftet.dk/files/a12190701_supplementary.pdf). Two were duplicates leaving 2,143 records. Among these, 1,839 records were excluded based on title and abstract leaving 304 records. After full text assessment, 271 records were excluded of which 21 were not of observational design, 165 were not about SH/ no information was provided on T3 or T4 in the definition of SH, one was an animal study, 26 did not concern AF, MI, HF or CVD mortality, 19 were guidelines or letters, five did not include euthyroid controls and 34 were inaccessible. This left 33 papers for review: 13 on AF, five on HF, 14 on MI, and 15 on CVD mortality.

Quality of studies

Studies were scored according to the NOS with a maximum possible score of nine. Scores are presented in **Table 1**, **Table 2**, **Table 3** and **Table 4**. All cohort studies (five on AF, five on HF, 11 on MI and 15 on CVD mortality) had a low risk of bias in selection of cohorts and comparability, and a medium risk of bias in outcome. All case control studies (all on AF, n = 4) had a low risk of bias in comparability of cases and controls and a medium risk of

bias in selection of cases and controls and exposure. Cross sectional studies on AF (n = 4) had a medium risk of bias in selection, comparability and outcome. Cross sectional studies on MI (n = 3) had a medium risk of bias in selection and outcome and a high risk of bias in comparability.

TABLE 1 / Overview of studies examining subclinical hyperthyroidism and atrial fibrillation.

Reference	TSH concentration, mIU/l	Population	Design Follow-up	n (%)	Age, yrs Gender	Effect estimate	Association	NOS[a]
Cappola et al, 2006 [11]	Grade 1: 0.1-0.44 Grade 2: ⟨ 0.1	Cardiovascular health study, background population, USA, age ⟩ 65 yrs	Cohort ~ 12.5 yrs	Total: 3,233 SH: 47 (1.5) Grade 1: 40 Grade 2: 7	~ 73 60% women	*Adjusted HR (95% CI)* 2.18 (1.42-3.33) Grade 1: 1.85 (1.14-3.00)	+	7
Gammage et al, 2007 [12]	⟨ 0.4	General practice, background population, UK, age ⟩ 65 yrs	Cross-sectional/ case-control	Total: 5,860 SH: 126 (2.2) TSH ⟨ 0.1: 27	~ 72 51% women	*Adjusted OR (95% CI)* 1.89 (1.01-3.57) *OR (95% CI)* The higher T4 the more AF: 1.08 (1.03-1.14) for a difference in T4 of 1 pmol/l	+	8
Nanchen et al, 2012 [16]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland and Ireland, outpatient clinic	Cohort ~ 3.5 yrs	Total: 5,316 SH: 71 (1.3)	~ 75 52% women	*Adjusted HR (95% CI)* 0.49 (0.16-1.53)	-	7
Rajao et al, 2019 [14]	⟨ 0.4	Baseline data from longitudinal study of adult health, ELSA-Brasil, background population, Brazil	Cross-sectional	Total: 1,795 SH: 193 (1.45)	~ 51 52% women	*OR* SH with AF: n = 0, therefore no OR p = 0.422	-	7
Takashima et al, 2007 [15]	⟨ 0.436	The Suita Study, background population, Japan	Cross-sectional	Total: 3,607 SH: 77 (2.13)	~ 69 65% women	*Prevalence* 3.98% vs 1.41% p ⟩ 0.05	-	3
Vadiveloo et al, 2011 [8]	Grade 1: 0.1-0.4 Grade 2: ⟨ 0.1	TEARS, background population, Scotland	Register-based, cohort ~ 5.6 yrs	Total: 12,155 SH: 2,004 Grade 1: 491 Grade 2: 414	~ 67 77% women	*Adjusted HR (95% CI)* Grade 1: 1.52 (1.11-2.08) Grade 2: 2.07 (1.30-3.29)	For all arrhythmias incl. AF: +	7
Auer et al, 2001 [9]	⟨ 0.4	Patients examined at or admitted to a hospital, Austria	Cross-sectional	Total: 23,638 SH: 613	~ 67 -	*Adjusted RR (95% CI)* 2.8 (1.3-5.8)	+	6
Selmer et al, 2012 [7]	⟨ 0.2 Reduced: 0.1-0.2 Suppressed: ⟨ 0.1	General practice, background population, Denmark, age ⟩ 18 yrs	Register-based cohort 5.5 yrs	Total: 586,460 SH: 6,276 (1.0)	~ 49 61% women	*Adjusted IRR (95% CI)* TSH ⟨ 0.2: 1.30 (1.18-1.43) Reduced TSH: 1.16 (0.99-1.36) Suppressed TSH: 1.41 (1.25-1.59)	+	8
Tenerz et al, 1990 [10]	⟨ 0.1	Outpatient clinic, Sweden	Cohort 2 yrs	Total: 80 SH: 40 (50)	65 88% women	*Prevalence* 28% (SH) vs 10% (euthyroid) p ⟨ 0.05	+	4
Aminorroaya et al, 2004 [18]	⟨ 0.3	Patients selected from a hospital, Iran	Case-control: AF and no AF	Total: 200 SH: 12 (6)	~ 60-62 49% women	*Prevalence* 6 (SH, AF) vs 6 (SH, no AF) p ⟩ 0.05	-	5
Jakowczuk et al, 2016 [17]	⟨ 0.1	Patients admitted with exacerbation of HF, Poland	Case-control: AF and no AF	Total: 120 SH: 2 (1.7)	~ 72-73 64% women	*Prevalence* 2 (SH, AF) vs 0 (SH, no AF) p = 0.0521	-	4
Rosario et al, 2016 [19]	Mild SH: 0.1-04	Subjects: outpatient clinic Controls: private clinic, Brazil Age ⟩ 65 yrs	Case-control: mild SH and euthyroid	Total: 180 SH: 90 (50)	73-74 100% women	*Prevalence* Known AF: 3.3% (SH) vs. 2.2% (euthyroid) Occult AF: 1/87 (SH) vs. 1/88 (euthyroid)	-	6
Wollenweber et al, 2013 [13]	0.1-0.44	Patients admitted with ischaemic stroke, Germany	Cohort/cross-sectional 3 mo.s	Total: 165 SH: 19 (11.5)	~ 70 43% women	*Prevalence* Baseline: 37% (SH) vs. 23% (euthyroid)	+	5

~: average.
AF = atrial fibrillation; CI = confidence interval; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; IRR = overall incidence rate ratio; NOS = Newcastle Ottawa Quality Assessment Scale; OR = odds ratio; PROSPER = Prospective Study of Pravastatin in Elderly at Risk of Cardiovascular Disease; SH = subclinical hyperthyroidism; T4 = free thyroxin; TEARS = Thyroid Epidemiology, Audit, and Research Study; TSH = thyroid-stimulating hormone.
a) Max. 9.

TABLE 2 / Overview of studies examining subclinical hyperthyroidism and heart failure.

Reference	TSH concentration, mIU/l	Population	Design Follow-up	n (%)	Age, yrs Gender	Effect estimate	Association	NOS[a]
Gencer et al, 2012 [21]	⟨ 4.5 Grade 1: 0.1-0.44 Grade 2: ⟨ 0.1	Outpatient clinic for HF and background population, USA and Europe	6 cohort studies ~ 10.4 yrs	Total: 25,390 SH: 648 (2.6)	~ 70 54% women	*Adjusted HR (95% CI)* TSH 0.1-0.44: 1.31 (0.88-1.95) TSH ⟨ 0.10: 1.94 (1.01-3.72)	+	7
Nanchen et al, 2012 [16]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland and Ireland, outpatient clinic	Cohort ~ 3.2 yrs	Total: 5,316 SH: 71 (1.3)	~ 75 52% women	*Adjusted HR (95% CI)* TSH ⟨ 0.1: 4.61 (1.71-12.47) TSH 0.1-0.45: 1.97 (0.63-6.17)	+	7
Rodondi et al, 2008 [22]	0.45-0.1 ⟨ 0.1	The Cardiovascular Health Study, background population, USA, age ⟩ 65 years	Cohort ~ 12 yrs	Total: 3,044 SH: 44 (1.4)	~ 73 60% women	*Adjusted HR (95% CI)* TSH ⟨ 0.45: 0.94 (0.48-1.83)	-	8
Selmer et al, 2014 [20]	⟨ 0.2 Grade 1: 0.1-0.2 Grade 2: ⟨ 0.1	General practice, background population, Denmark, age ⟩ 18 years	Register-based, cohort ~ 5.5 yrs	Total: 563,700 SH: 5,979 (1.1)	~ 47 61% women	*Adjusted IRR (95% CI)* TSH ⟨ 0.2: 1.20 (1.10-1.31) Grade 1: 1.20 (1.04-1.38) Grade 2: 1.20 (1.07-1.34)	+	8
Asvold et al, 2012 [23]	⟨ 0.49	HUNT 2, background population, Norway	Cohort ~ 12.3 yrs	Total: 26,707 SH: 524	~ 54 68% women	*Adjusted HR (95% CI)* TSH ⟨ 0.49: 1.52 (0.86-2.69)	-	6

~: average.

CI = confidence interval; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; HUNT = the Nord-Troendelag Health Study; IRR = overall incidence rate ratio; NOS = The Newcastle Ottawa Quality Assessment Scale; PROSPER = Prospective Study of Pravastatin in Elderly at Risk of Cardiovascular Disease; SH = subclinical hyperthyroidism; TSH = thyroid-stimulating hormone.

a) Max. 9.

TABLE 3 / Overview of studies examining subclinical hyperthyroidism and myocardial infarction.

Reference	TSH concentration, mIU/l	Population	Design Follow-up	n (%)	Age, yrs Gender	Effect estimate	Association	NOS[a]
Afsar et al, 2017 [25]	⟨ 0.35	Renal Unit of the Gulhane School of Medicine Medical Center, Ankara, Turkey, chronic kidney disease	Cohort ~ 29 mo.s	Total: 292 SH: 27 (9.2)	~ 57 56% women	*CVE, n (%)* SH: 3 (11.1) *Adjusted HR (95% CI)* 4.62 (0.70-27.25)	-	6
Cappola et al, 2006 [11]	Grade 1: 0.1-0.44 Grade 2: ⟨ 0.1	Cardiovascular Health Study, background population, USA, age ⟩ 65 yrs	Cohort ~ 12.5 yrs	Total: 3,233 SH: 47 (1.5) Grade 1: 40 Grade 2: 7	~ 73 68% women	*Adjusted HR (95% CI)* 1.18 (0.74-1.88)	-	7
Golledge et al, 2018 [24]	⟨ 0.4 Elderly-adjusted: ⟨ 0.67[e]	The Health in Men Study, background population, Western Australia	Cohort ~ 9.5 yrs	Total: 3,712 SH: 27 (0.7) SH elderly: 91 (2.5)	~ 76 100% men	*Adjusted HR (95% CI)* T4, upper quartile vs lower quartiles: 1.29 (1.06-1.59)	- + high T4 and MI	7
Nanchen et al, 2012 [16]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland, and Ireland, outpatient clinic	Cohort ~ 3.2 yrs	Total: 5,316 SH: 71 (1.3)	~ 75 52% women	*Adjusted HR (95% CI)* 0.84 (0.37-1.88)	-	6
Selmer et al, 2014 [20]	⟨ 0.2 Grade 1: 0.1-0.2 Grade 2: ⟨ 0.1	General practice, background population, Denmark, age ⟩ 18 yrs	Register-based cohort ~ 5.5 yrs	Total: 563,700 SH: 5,979 (1.1)	~ 47 61% women	*Adjusted IRR (95% CI)* TSH ⟨ 0.2: 1.02 (0.89-1.18) Grade 1: 1.13 (0.92-1.39) Grade 2: 0.95 (0.79-1.15)	-	8
Tohidi et al, 2018 [26]	⟨ 0.34	Tehran Thyroid Study, background population, Iran, age ⟩ 30 yrs	Cohort ~ 11.2 yrs	Total: 3,975 SH: 145 (3.6)	~ 47 56% women	*Adjusted HR (95% CI)* 0.71 (0.37-1.33)	-	8
Gill et al, 2013 [27]	⟨ 0.4	E-ECHOES, Southeast Asian and African-Caribbean minorities in the background population, GB, age ⟩ 45 yrs	Cross-sectional substudy of former screening programme for HF within minorities	Southeast Asian: 1,111 African-Caribbean: 763 SH: 54 (2.9)	*Southeast Asian* ~ 58, 44% women *African-Caribbean* ~ 59, 56% women	*Prevalence, n* 87 (MI, euthyroidism) vs 2 (MI, SH) p = 0.91	-	4
Takashima et al, 2007 [15]	⟨ 0.436	The Suita Study, background population, Japan	Cross-sectional	Total: 3,607 SH: 77 (2.13)	~ 69 45% women	*MI* 2.6% vs 1.28% p ⟩ 0.05	-	3
Walsh et al, 2005 [31]	⟨ 0.4	Busselton Health Study, background population, Western Australia	Cohort ~ 20 yrs	Total: 2,108 SH: 39 (1.9)	~ 50 50% women	*Adjusted HR (95% CI)* CVE[c]: 1.0 (0.4-2.5)	-	9
Sgarbi et al, 2010 [30]	⟨ 0.45	The Japanese-Brazilian thyroid study, Japanese-Brazilian Bauru[b], Brazil, age ⟩ 30 yrs	Cohort ~ 7.5 yrs	Total: 1,110 SH: 69 (6.2)	~ 57 53% women	*CVD[d], n (%)* 120 (13.1) vs 13 (18.8) (SH) p ⟩ 0.05	-	5
Drechsler et al, 2014 [32]	⟨ 0.3	4D, diabetic haemodialysis patients, Germany	Cohort ~ 4 yrs	Total: 1,000 SH: 137 (13.7)	~ 66 57% women	*Adjusted HR (95% CI)* 1.38 (0.90-2.01)	-	6
Asvold et al, 2012 [23]	⟨ 0.49	HUNT 2, background population, Norway	Cohort ~ 12.2 yrs	Total: 26,707 SH: 524 (2)	~ 54 68% women	*Adjusted HR (95% CI)* 1.37 (0.91-2.05)	-	6
Martin et al, 2017 [28]	⟨ 0.56	ARIC, background population, USA	Cohort ~ 22.5 yrs	Total: 11,359 SH: 378 (3.3)	~ 57 58% women	*Adjusted HR (95% CI)* 1.14 (0.83-1.58)	-	7
Zijlstra et al, 2020 [29]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland and Ireland, outpatient clinic	Cohort 3.2 yrs	Total: 4,864 SH: 109 (2.2)	~ 75 51% women	*Adjusted HR (95% CI)* Coronary heart disease death or non-fatal MI or fatal/non-fatal stroke: 0.51 (0.24-1.07)	-	7

~: average.
4D = Die Deutsche Diabetes Dialyse Studie; ARIC = Atherosclerosis Risk in Communities Study; CI = confidence interval; CVD = cardiovascular disease; CVE = cardiovascular events; E-ECHOES = The Ethnic-Echocardiographic Heart of England Screening Study; HF = heart failure; HR = hazard ratio; HUNT = The Nord-Troendelag Health Study; IHD = ischaemic heart disease; IRR = overall incidence rate ratio; MI = myocardial infarction; NOS = The Newcastle Ottawa Quality Assessment Scale; PROSPER = Prospective Study of Pravastatin in Elderly at Risk of Cardiovascular Disease, SH = subclinical hyperthyroidism; T4 = free thyroxin; TSH = thyroid-stimulating hormone.
a) Max. 9.
b) Human Development Index = 0.825.
c) Acute and chronic IHD, MI, angina.
d) MI, angioplasty, revascularisation, coronary insufficiency, stroke.
e) T4 concentration: 10-23 pmol/l.

TABLE 4 / Overview of studies examining subclinical hyperthyroidism and cardiovascular mortality.

Reference	TSH concentration, mIU/l	Population	Design Follow-up	n (%)	Age, yrs Gender	Effect estimate	Association	NOS[a]
Cappola et al, 2006 [11]	Grade 1: 0.1-0.44 Grade 2: ⟨ 0.1	Cardiovascular Health Study, background population, USA, age ⟩ 65 yrs	Cohort ~ 12.5 yrs	Total: 3,233 SH: 47 (1.5) Grade 1: 40 Grade 2: 7	~ 73 68% women	*Adjusted HR (95% CI)* 1.02 (0.53-1.98)	-	8
Ceresini et al, 2013 [34]	⟨ 0.46	InCHIANTI, background population, Italy, age ⟩ 65 yrs	Cohort ~ 6 yrs	Total: 951 SH: 83 (8) TSH ⟨ 0.1: 16	⟩ 65 57% women	*Adjusted HR (95% CI)* 1.72 (0.82-3.64)	-	9
Golledge et al, 2018 [24]	⟨ 0.4 Elderly-adjusted: ⟨ 0.67[c]	The Health in Men Study, background population, Western Australia, elderly	Cohort ~ 9.5 yrs	Total: 3,712 SH: 27 (0.7) SH, elderly: 91 (2.5)	~ 76 100% men	*HR (95% CI)* T4, upper quartile vs lower quartiles: Unadjusted: 1.36 (1.14-1.63) Adjusted: 1.08 (0.89-1.32)	-	8
Nanchen et al, 2012 [16]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland and Ireland, outpatient clinic	Cohort ~ 3.2 yrs	Total: 5,316 SH: 71 (1.3)	~ 75 52% women	*Adjusted HR (95% CI)* TSH ⟨ 0.45: 1.33 (0.50-3.59) TSH ⟨ 0.1: 2.79 (0.89-8.74)	-	7
Parle et al, 2001 [33]	⟨ 0.5	Background population, England and Wales	Cohort ~ 8.2 yrs	Total: 1,209 SH: 71 (6)	~ 70 56% women	*HR (95% CI)* Follow-up at 5 yrs: 2.2 (1.1-4.4) End of follow-up: 1.4 (0.8-2.6)	+ / -	9
Schultz et al, 2011 [36]	⟨ 0.4	Frederiksberg Heart Failure Study, background population, Denmark, age ⟩ 50 yrs	Cohort ~ 5 yrs	Total: 609 SH: 25 (4.1)	~ 70 57% women	*HR (95% CI)* Unadjusted: 2.38 (1.10-5.18) Adjusted: 1.96 (0.88-4.35)	-	8
Sgarbi et al, 2010 [30]	⟨ 0.45	The Japanese-Brazilian thyroid study, Japanese-Brazilians, Bauru[b], Brazil, age ⟩ 30 years	Cohort ~ 7.5 yrs	Total: 1,110 SH: 69 (6.2)	~ 57 53% women	*HR (95% CI)* Unadjusted: 4.5 (2.1-10.1) Adjusted: 3.7 (1.6-6.4)	+	8
Pearce et al, 2016 [35]	⟨ 0.399	Newcastle 85+ Study, nursing home and general practice, UK, age ⟩ 85 yrs	Cohort ~ 9 yrs	Total: 643 SH: 19 (2.9)	~ 86 58% women	*Kaplan-Meier curve* p = 0.94 for men p = 0.18 for women	-	8
Walsh et al, 2005 [31]	⟨ 0.4	Busselton Health Study, background population, Western Australia	Cohort ~ 20 ars	Total: 2,108 SH: 39 (1.8)	~ 50 52% women	*Adjusted HR (95% CI)* 1.1 (0.3-3.4)	-	9
Asvold et al, 2012 [23]	⟨ 0.49	HUNT 2, background population, Norway	Cohort ~ 12.3 yrs	Total: 26,707 SH: 524 (2)	~ 54 68% women	*Adjusted HR (95% CI)* 1.60 (0.96-2.68)	-	7
Drechsler et al, 2014 [32]	⟨ 0.3	4D, diabetic haemodialysis patients, Germany	Cohort ~ 4 yrs	Total: 1,000 SH: 137 (13.7)	~ 66 57% women	*Adjusted HR (95% CI)* 1.51 (0.96-2.38)	-	7
Frey et al, 2013 [37]	⟨ 0.3	INH, hospitalised patients with HF and EF ⟨ 40%, South Germany	Cohort 3 yrs	Total: 744 SH: 69 (9)	~ 68 29% women	*Adjusted HR (95% CI)* 1.18 (0.74-1.90)	-	6
Hayashi et al, 2016 [39]	⟨ 0.45	Patients with acute decompensated heart failure, Japan	Cohort ~ 2.7 yrs	Total: 274 SH: 5 (2)	~ 70 43% women	*HR* SH and cardiac death: n = 0, therefore no HR	-	4
Wang et al, 2015 [38]	⟨ 0.55	Idiopathic dilated cardiomyopathy, China	Cohort ~ 17 mo.s	Total: 458 SH: 35 (7.6)	~ 51 29% women	*Adjusted HR (95% CI)* 0.941 (0.43-2.05)	-	6
Zijlstra et al, 2020 [29]	⟨ 0.45	PROSPER, elderly with CVD risk factors or a history of CVD, the Netherlands, Scotland and Ireland, outpatient clinic	Cohort ~ 3.2 yrs	Total: 4,864 SH: 109 (2.2)	51% women	*Adjusted HR (95% CI)* Coronary heart disease death or non-fatal MI or fatal/non-fatal stroke: 0.51 (0.24-1.07)	-	7

~: average.
4D = Die Deutsche Diabetes Dialyse Studie (the German diabetes dialysis study); CI = confidence interval; CVD = cardiovascular disease; EF = ejection fraction; HR = hazard ratio; HUNT = The Nord-Troendelag Health Study; InCHIANTI = Invecchiare in Chianti ("aging in the Chianti area"); INH = interdisciplinary Network Heart Failure study; MI = myocardial infarction; NOS = The Newcastle Ottawa Quality Assessment Scale; PROSPER = PROspective Study of Pravastatin in Elderly at Risk of Cardiovascular Disease; SH = subclinical hyperthyroidism; T4 = free thyroxin; TSH = thyroid-stimulating hormone.
a) Max. 9.
b) Human Development Index = 0.825.
c) T4 concentration: 10-23 pmol/l.

Atrial fibrillation

The literature search identified 13 observational studies that investigated the association between SH and AF. The studies are presented in Table 1.

Three larger studies investigated the risk of AF in patients with SH. Selmer et al [7] studied the risk of AF in a large cohort of subjects from primary care in Denmark. Subjects were excluded if they had a history of AF or thyroid illness. The study included 6,276 subjects with SH. The overall incidence rate ratio (IRR) was 1.30 (95% confidence interval (CI): 1.18-1.43) adjusted for sex, age, calendar year, the Charlson Comorbidity Index and

socioeconomic status. Vadiveloo et al [8] examined patients from general practices and categorised them according to the severity of SH (grade one: TSH level 0.1-0.4 mIU/l, grade two: TSH level < 0.1 mIU/l). They found an adjusted hazard ratio (HR) of 1.52 (95% CI: 1.11-2.08) for AF and other arrhythmias and an adjusted HR of 2.07 (95% CI: 1.30-3.29) for patients with grade one and two SH, respectively. Six months after diagnosis of SH, patients with persistent SH still had an increased risk of arrhythmias including AF. Auer et al [9] performed a cross sectional analysis on inpatients in Austria. The population consisted of 23,638 subjects of whom 613 patients suffered from SH. Patients taking thyroid hormone replacement were excluded. After adjusting for age and known risk factors for AF including hypertension, left ventricular hypertrophy and underlying structural heart disease, they found a relative risk (RR) of 2.8 (95% CI: 1.3-5.8) of AF in patients with SH.

Four studies with fewer participants also showed an association between SH and AF: In an early study from 1990, Tenerz et al [10] showed an increased number of AF in SH patients selected from an outpatient clinic with an AF prevalence of 28% versus 10% in euthyroid controls ($p < 0.05$). Cappola et al [11] investigated patients from the general population in the USA among individuals with a health insurance. After adjusting for age, sex, clinical CVD at study start, AF risk factors and thyroidal medication during the study, SH was associated with AF with a HR of 1.98 (95% CI: 1.29-3.03). Gammage et al [12] studied elderly patients who received no thyroidal medication and had no history of hyperthyroidism. They reported an odds ratio (OR) of 1.89 (95% CI: 1.01-3.57) when adjusted for AF risk factors. Furthermore, the authors found that the presence of AF was associated with the T4 concentration (OR: 1.08 (95% CI: 1.03-1.14) per 1 pmol/l T4 increase). Wollenweber et al [13] investigated patients with ischaemic stroke and found a higher prevalence of AF in patients with SH (37%) versus euthyroid patients (23%).

Six studies reported no association between SH and AF. Two of the studies were cross-sectional studies, [14, 15]. One study examined a population with a heavy CVD risk profile or heavy CVD co-morbidity, making it possible that these patients developed AF for other reasons than SH [16]. Two studies examined patients with AF in a case-control design finding no differences in the number of subjects with SH in the groups with or without AF (n = 12 and n = 2, respectively) [17, 18]. One case-control study found a similar prevalence of AF in subjects with SH (n = 1/87) and euthyroid subjects (n = 1/88) [19].

Heart failure

The literature search produced five observational studies on SH and HF. The studies are presented in Table 2.

Selmer et al [20] reported data from a large Danish cohort, n = 563,700, of whom 5,979 had SH. All participants were without thyroid disease or CVD at inclusion. Results were adjusted for age, sex and AF at both study start and during the follow-up period, but not for blood pressure or smoking as these factors were unknown. The authors found an increased risk of developing HF in SH patients with an IRR of 1.20 (95% CI: 1.10-1.31), but no evidence of a dose-response relationship with the grade of SH.

Gencer et al [21] reported on patients from the general population and from an outpatient clinic for HF and found a borderline significantly increased risk of HF (HR: 1.46 (95% CI: 0.94-2.27)) in age- and sex-adjusted analyses among patients with TSH level < 0.45 mIU/l. The association was carried by a significantly increased risk among individuals with TSH level < 0.1 mIU/l (HR: 1.94 (95% CI: 1.01-3.72)). When adjusting for risk factors for HF, a trend towards the same results persisted (HR: 1.92 (95% CI: 0.99-3.71)) in the group of patients with TSH level < 0.1 mIU/l.

Nanchen et al [16] explored elderly patients with either a history of CVD or CVD risk factors; among these, 71 participants had SH. They found that SH patients had an increased risk of developing HF, particularly patients with TSH level < 0.1 mIU/l (age and sex adjusted HR: 4.61 (95% CI: 1.71-12.47)).

In contrast to these studies, Rodondi et al [22] found no increased risk of developing HF in SH (n, SH = 44). Asvold et al [23] investigated a cohort of the Norwegian general population including 524 patients with SH and found no association between HF and SH in analyses adjusted for age, smoking, BMI and sex (HR: 1.52 (95% CI: 0.86-2.69)).

Myocardial infarction

The literature search produced 14 observational studies about SH and MI. The studies are presented in Table 3.

Golledge et al [24] explored the association between TSH and T4, respectively, and the incidence of new-onset CVD in elderly men with no history of thyroid dysfunction. They found no increased risk of MI when using the traditional definition of SH (low-level TSH and normal levels of T4 and T3). However, a significant association between T4 in the upper reference range and an increased risk of developing MI appeared with an adjusted HR of 1.29 (95% CI: 1.06-1.59).

Afsar et al [25] investigated patients with chronic kidney disease and SH and their risk of developing coronary heart disease. There was an increased risk of cardiovascular events (acute MI, angina pectoris, and need for by-pass surgery) with a HR of 4.83 (95% CI: 1.13-20.66) when adjusted for age, sex, hypertension, diabetes and smoking. When adjusting for haemoglobin, estimated glomerular filtration rate, fibroblast growth factor-23, high-sensitive C-reactive protein, and high-density lipoprotein-cholesterol, the results became insignificant.

The literature search revealed another 12 studies that failed to find an association between MI and SH [11, 15, 16, 20, 23, 26-32]. Selmer et al [20], Asvold et al [23] and Martin et al [28] investigated large cohorts of the general population in Denmark, Norway, and USA, respectively, and found no association between MI and SH (adjusted IRR: 1.02 (95% CI: 0.89-1.18), adjusted HR: 1.37 (95% CI: 0.91-2.05) and adjusted HR: 1.14 (95% CI: 0.83-1.58), respectively).

Cardiovascular mortality

The literature search produced 15 observational studies investigating SH and CVD mortality. The studies are presented in Table 4.

After 7.5 years of follow-up, Sgarbi et al [30] found an increased risk of CVD mortality with an unadjusted HR of 4.5 (95% CI: 2.1-10.1) in patients with SH compared with euthyroid participants. The increased risk persisted after adjustment for age, sex, smoking and other factors. However, the study is limited by the small number of deaths (n = 14) of which only eight were due to CVD.

Parle et al [33] found an increased risk of CVD mortality in SH from year one to five during follow-up (adjusted HR = 2.2 (95% CI: 1.1-4.4)). At the end of the study (an average of eight years of follow-up), a borderline significantly increased risk persisted. Drechsler et al [32] investigated the risk of sudden cardiac death in diabetic haemodialysis patients with SH and found similar results with a borderline statistically significantly increased risk at the end of follow-up (adjusted HR: 1.51 (0.96-2.38)).

The remaining studies found no association between SH and CVD mortality [11, 16, 23, 24, 29, 31, 34-39]. Asvold et al [23] presented the largest cohort of 524 patients with SH and found a HR of death from coronary heart disease of 1.60 (95% CI: 0.96-2.68) adjusted for age, sex, BMI, and smoking, but the results only reached borderline significance. Zijlstra et al [29] studied the effect of persistent SH (defined as SH in two blood analyses taken at a six-month interval) on a combined endpoint of death from coronary heart disease, MI and stroke and found a HR of 0.51 (95% CI: 0.24-1.07) in a multivariate adjusted analysis indicating a decreased risk. However, the result was only borderline significant.

DISCUSSION

In summary, the systematic literature search presented above supports an association between SH and AF, which is in line with prior reviews and meta-analyses [40, 41]. Five studies add to the evidence on this association. In particular, the larger studies support an association [7-9]. However, Vadiveloo et al investigated arrhythmias in general and not AF specifically [8]. Studies that reported no association between SH and AF were generally of a weaker design (e.g., cross-sectional), reported on smaller cohorts, or had very few events of AF, suggesting lack of power to detect an actual difference. A Mendelian randomisation study investigating the association between thyroid dysfunction and CVD found evidence of a causal association of SH and AF, supporting this association [42]. Gammage et al [12] found that the risk of AF increased with a higher level of T4 within the reference range. This is in contrast to the findings of a Mendelian randomisation study investigating the effect of different thyroid parameters on AF not supporting an association of AF with increased T4 within the reference range [43]. Sawin et al [44] analysed data from the Framingham Heart Study (background population, USA) and found a RR of AF in patients > 60 years of age with TSH level < 0.4 mIU/l of 3.0 (95% CI: 1.7-5.5) after ten years of follow-up. The result was adjusted for T4 and other factors, indicating that the risk of AF is increased due to TSH concentration independently of T4. It should be mentioned that Sawin et al included both SH and hyperthyroid subjects in their analysis.

Our review mainly supports an association between SH and an increased risk of HF. Selmer et al [20] performed a large register-based cohort study in Denmark providing results supporting an association between SH and HF. However, it was not possible to adjust for smoking in this study, which affects both the risk of thyroid disease and CVD. Asvold et al [23] and Gencer et al [21] performed studies similar to each other but came to different conclusions. Gencer et al found an increased risk of HF in patients with TSH level < 0.1 mIU/l. Asvold et al only studied patients with SH as a whole and found an increased risk of HF, but this risk was not statistically significant. This may suggest that AF development depends on the grade of SH. In addition, Gencer et al included patients from an outpatient clinic for HF, suggesting that patients with HF may be more sensitive to SH. Another possible explanation for this observation is that patients with various co-morbidities are followed in outpatient clinics, and blood sampling (including thyroid screening) may therefore be performed more frequently than in healthier subjects not followed in a clinic, indicating surveillance bias. It is also of note that AF and HF are closely associated diseases. Therefore, it is possible that the increased risk of HF is caused by an increased risk of AF or vice versa. However, whether such a relationship exists cannot be elucidated from any of these studies.

Only two studies reported an increased risk of MI in SH patients [24, 25]. However, they both had significant limitations since MI was only a secondary endpoint in one study [24] and MI was not analysed as an independent endpoint in the other [25]. The literature search revealed 12 studies that found no association between SH and MI. Consequently, the current literature does not support an association between SH and MI. A meta-analysis found an association between coronary heart disease and SH, but MI was not investigated separately [45]. This also applies to many of the studies included in our review; several studies analysed MI as a combined endpoint with chronic ischaemic heart disease, stroke or cardiac death, making it difficult to assess the risk of MI independently.

Our review contains only scarce evidence of a potential association between SH and CVD mortality. The literature search produced a somewhat large number of studies on the risk of SH and CVD mortality not supporting an association between the two. However, most studies comprised populations with fewer than 100 subjects with SH, suggesting that the studies may be underpowered. In addition, the study populations were heterogeneous (e.g., patients with diabetes receiving haemodialysis and patients with cardiovascular morbidity) and thus their findings may not be applicable to the general population. They were also different regarding the endpoints, e.g., cardiac death defined solely as death from coronary heart disease or solely from ventricular arrhythmia/congestive HF or not further specified. One study even combined the endpoint death from coronary

heart disease with non-fatal MI and stroke. The various definitions on CVD mortality complicate any definite conclusions, but overall, our findings do not support an association between SH and CVD mortality. A number of reviews/meta-analyses already exist exploring the risk of CVD mortality in patients with SH, but results are conflicting. Most reported either no increased risk of CVD mortality in patients with SH [46, 47] or data were insufficient to draw any definite conclusions [40, 48]. One meta-analysis [49] found an increased risk but the risk was significant only in subgroup analyses of studies with convenience sampling on cardiac patients, chronically ill geriatric patients and patients with acute cardiac disease. However, surveillance bias may also be a possible explanation for this observation.

As all the present studies are of observational design, it is unknown whether treatment of SH will reduce the risk of AF and HF. Antithyroid treatment is associated with different side effects including minor and transient ones but also potentially life-threatening adverse effects even though these are rare. Since the overall risk of adverse effects of medical treatment seems negligible [2], treatment of endogenous SH (radioactive iodine for multi nodular toxic goiter/antithyroid drugs for Graves' disease) may seem reasonable in light of the observed association with AF and HF, especially in elderly patients. This is also in accordance with the present European guidelines [2]. SH is associated with severe disease and therefore should be regarded a biochemically milder form of thyrotoxicosis but with the same physiological consequences, supporting that medical treatment should be considered.

CONCLUSIONS

The current literature does not provide convincing evidence of an association between SH and MI or cardiovascular death. In contrast, evidence seems to support an association between SH and AF and HF, respectively. Future randomised intervention trials are needed in order to support a possible causal relationship between SH and AF and HF, respectively, and to determine whether treatment of SH reduces the risk of AF and HF.

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