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1. Einleitung

Meine Doktorarbeit beschäftigt sich mit dem Thema Epidemiologie von Schilddrüsenerkrankungen in einer ehemaligen Jodmangelregion. Ausgewertet wurden hierzu Daten der Study of Health in Pomerania (SHIP). Jodmangelregionen sind durch erhöhte Prävalenzen von Struma [1, 2] und Schilddrüsenüberfunktion (Hyperthyreose) [3] charakterisiert. Ostvorpommern ist, wie auch Deutschland insgesamt, ein ehemaliges Jodmangelgebiet [4]. Aus diesem Grund weist Ostvorpommern eine hohe Prävalenz an endemischer Struma auf [2]. Vor der Wiedervereinigung Deutschlands wurde in der Deutschen Demokratischen Republik, und somit auch in Ostvorpommern, 1983 die generelle Jodprophylaxe eingeführt. Diese zeigte bis 1989 Wirkung, führte aber nicht dazu, dass der Jodmangel bis 1989 beseitigt wurde [5]. Der Effekt ging nach der Wiedervereinigung zunächst verloren [5]. Erst Ende 1993 wurde eine optimierte Gesetzgebung bezüglich der Jodierung des Tafelsalzes in Gesamtdeutschland eingeführt. Seither wird überwiegend Jodsalz in der Nahrungsmittelproduktion verwendet. Daraus resultierend stieg die mediane Jodausscheidung in der Studienregion auf 124 µg/l [4]. Des Weiteren wurde in einer deutschlandweiten, an Kindern und Heranwachsenden durchgeführten Studie eine mediane Jodausscheidung von 117 µg/l festgestellt [6]. Die Ergebnisse dieser beiden Studien weisen darauf hin, dass Deutschland mittlerweile kein Jodmangelgebiet mehr ist und sich die Jodversorgung der Bevölkerung in einem unteren wünschenswerten Bereich befindet.

In dem ersten Teil meiner Arbeit habe ich mich mit dem Zusammenhang von Rauchverhalten und 5-Jahres-Inzidenz der Struma beschäftigt. Sollte kein Zusammenhang zwischen dem Rauchverhalten und inzidenter Struma bestehen, so würde dies für eine ausreichende Jodversorgung in der Studienregion sprechen [1]. Ferner habe ich den Zusammenhang zwischen subklinischen Schilddrüsenfunktionsstörungen und kardiovaskulären Endpunkten (arterielle Hypertonie und Mortalität) untersucht. Ein Nachweis solcher Assoziationen hätte zur Folge, dass bereits bei subklinischen Veränderungen der Schilddrüsenfunktion therapiert werden sollte. Im Folgenden wird nun spezifisch auf die Problemstellungen der drei Arbeiten, auf dessen Grundlage meine Doktorarbeit entstanden ist, eingegangen.

1.1 Der Einfluss des Rauchens auf die Struma-Progression

Die Rolle des Rauchens in der Pathogenese von Struma wird derzeitig kontrovers diskutiert. Es wird vermutet, dass das Rauchen sich in Jodmangel-Regionen stärker auf die Entwicklung der Struma auswirkt als in Regionen mit ausreichender Jodversorgung [1, 7-9]. Zwei Studien [2, 10], die in Jodmangel-Regionen durchgeführt worden sind, wiesen einen Zusammenhang zwischen Rauchen und Struma nach, wohingegen eine andere Studie aus einer Jodmangel-Region [11] keinen Zusammenhang gefunden hat. Auch die Ergebnisse aus Regionen mit ausreichender Jodversorgung sind widersprüchlich. Einige dieser Studien [12, 13] konnten einen Zusammenhang zwischen Rauchen und Struma nachweisen, andere [14, 15] hingegen nicht. Die meisten bisher durchgeführten Studien [1, 2, 7, 10-15] sind limitiert in ihrer Aussagekraft, weil sie im Querschnitt durchgeführt worden sind und somit keine Aussage in Hinblick auf die Kausalität aufzeigen konnten. Lediglich eine Studie [9] verwendete ein prospektives Kohortendesign, allerdings wurden in dieser Studie nur schwangere Frauen untersucht.

Im Nordosten Deutschlands wurde Mitte der neunziger Jahre die Jodversorgung durch Hinzugabe von jodiertem Salz in die Nahrungsmittelproduktion verbessert. Dieses führte zu der paradoxen Situation einer hohen Struma-Prävalenz in einer Region mit ausreichender Jodversorgung. Eine dänische Studie, die das Schilddrüsenwachstum zwischen Regionen mit milder und moderater Jodversorgung verglichen hat, kam zu dem Ergebnis, dass jüngere Individuen mehr von einer besseren Jodversorgung profitieren als ältere [1].

Im Rahmen von SHIP wurde im Querschnitt ein Zusammenhang zwischen Rauchen und Struma demonstriert [2]. Nun ist es interessant zu überprüfen, ob ebenfalls ein Zusammenhang zwischen Rauchen und inzidenter Struma existiert. Würde sich der Befund aus der Querschnittsanalyse bestätigen, so wäre dies ein Indiz dafür, dass in der Studienregion weiterhin ein Jodmangel persistiert, da der Einfluss des Rauchens auf die Entwicklung von Struma mit steigender Jodversorgung abnehmen sollte.

1.2 Zusammenhang zwischen subklinischer Hyperthyreose und inzidenter arterieller Hypertonie in einer populationsbasierten Kohortenstudie

Die Art des Zusammenhanges zwischen subklinischer Hyperthyreose und Blutdruck wird kontrovers diskutiert. Vorherige Studien haben Assoziationen von subklinischer Hyperthyreose zu kardiovaskulären Endpunkten wie endotheliale Dysfunktion [16], linksventrikuläre Hypertrophie [17, 18], Wanddicke der Carotis [19] und Vorhofflimmern [20, 21]

aufgezeigt. Das Vorhandensein dieser Assoziationen könnte auf eine direkte Funktionsstörung der Schilddrüsenhormone zurückzuführen sein. Es besteht jedoch ebenfalls die Möglichkeit, dass diese Assoziationen vorliegen, weil eine subklinische Hyperthyreose mit einer arteriellen Hypertonie einher geht. Der Zusammenhang zwischen subklinischer Hyperthyreose und Blutdruck wurde in letzter Zeit in mehreren populations-basierten Studien untersucht [22-26]. Von diesen vier Studien konnte nur eine einen Zusammenhang zwischen subklinischer Hyperthyreose und Hypertonie nachweisen [26].

Eine Limitation aller bisherigen Studien [22-26] ist, dass diese den Zusammenhang zwischen subklinischer Hyperthyreose und Hypertonie nur im Querschnittsdesign untersucht haben. Dieser Studientyp lässt keine Aussage über Ursache und Wirkung zu, und kann daher zu falschen Entscheidungen hinsichtlich der Behandlung von Patienten führen. Wenn man nun in einem longitudinalen Design einen Zusammenhang zwischen subklinischer Hyperthyreose und inzidenter Hypertonie nachweisen könnte, so würde dieses einen Einfluss auf die momentane Diskussion haben, ob ein Patient mit subklinischer Hyperthyreose behandelt und ab welchem Thyroidea-stimulierendem Hormon (TSH) Wert mit einer Behandlung begonnen werden sollte [27, 28].

Aus diesem Grund wurde hier der Zusammenhang zwischen subklinischer Hyperthyreose und der Veränderung im Blutdruck (systolischer Blutdruck, diastolischer Blutdruck und Blutdruckamplitude) über einen Zeitraum von 5 Jahren in einer populations-basierten Kohortenstudie untersucht.

1.3 Zusammenhang zwischen erniedrigtem Thyreoidea-stimulierendes Hormon (TSH) und Mortalität

Ein Zusammenhang zwischen erniedrigtem TSH und Mortalität könnte durch mehrere Mechanismen erklärt werden. So wurde berichtet, dass erniedrigtes TSH mit Surrogatmarkern für kardiovaskuläre Mortalität wie Wanddicke der Carotis [19], Vorhofflimmern [20, 21], erhöhte Plasma-Fibrinogen-Spiegel [29] und linksventrikuläre Hypertrophie [17, 18] assoziiert ist. Die Ergebnisse bisheriger Studien zur Assoziation zwischen erniedrigtem TSH bzw. subklinischer Hyperthyreose und Mortalität [21, 26, 30-40] sind widersprüchlich. Bezüglich kardiovaskulärer Mortalität haben die meisten Studien [21, 33, 34, 41] und Meta-Analysen [33, 37, 40] keinen Zusammenhang gefunden, wohingegen drei Studien [30, 32, 42] einen Zusammenhang nachweisen konnten.

Im Hinblick auf die Gesamt-Mortalität konnte eine Studie erniedrigtes Serum TSH als Risikofaktor für Mortalität identifizieren [30], wohingegen zwei Studien [35, 39] dieses nicht konnten. Bezüglich subklinischer Hyperthyreose haben die meisten Studien [21, 32, 38, 41] keinen Zusammenhang zwischen Schilddrüsenüberfunktion und Gesamt-Mortalität detektiert. Lediglich eine Studie, durchgeführt mit geriatrischen Patienten [36], konnte eine solche Assoziation zeigen. Des Weiteren deckte eine Studie [34] einen Zusammenhang zwischen einer manifesten Hyperthyreose und Gesamt-Mortalität auf. Unterschiedliche Ergebnisse könnten auf Nichtberücksichtigung von wichtigen Confoundern [30, 34, 35], unterschiedlichen Definitionen von Hyperthyreose, Unterschieden in der Follow-Up Zeit oder die Wahl der Studienpopulation zurückzuführen sein. Ferner haben einige Studien [30, 32, 35] eine subklinische nicht von einer manifesten Hyperthyreose unterschieden. Diese Kontroverse wird durch den Umstand, dass sogar Meta-Analysen zu unterschiedlichen Ergebnissen gelangen, verstärkt. Obwohl eine Meta-Analyse [31] einen Zusammenhang nachweisen konnte, wurde dieses Ergebnis von drei weiteren Meta-Analysen [33, 37, 40] nicht bestätigt.

Bezüglich der Assoziation zwischen Hyperthyreose und Krebs-Mortalität haben alle bisher vorliegenden Studien [43-48] Personen nach Radiojodbehandlung mit gesunden Personen verglichen. Von diesen Studien haben drei einen positiven [45, 46, 48], eine einen inversen [44] und zwei [43, 47] keinen Zusammenhang zwischen Hyperthyreose und Krebs-Mortalität festgestellt.

Zusammengefasst ist der derzeitige Wissensstand hinsichtlich einer möglichen Assoziation zwischen erhöhter Schilddrüsenfunktion und Mortalität schwach und inkonsistent [33, 37, 40]. Aus diesem Grund wurde dieser Zusammenhang in SHIP untersucht.

2. Material und Methoden

2.1 Studienpopulation

Die der Arbeit zugrundeliegenden Daten stammen aus der populationsbasierten Kohortenstudie SHIP. Die Studienregion von SHIP umfasst die Städte Greifswald, Stralsund und Anklam sowie 29 umgebende Kommunen. Insgesamt lebten im Jahre 1997 212.157 Einwohner in der Studienregion. Von diesen wurden für Baseline-SHIP 7008 Individuen im Alter von 20 – 80 Jahren aus dem Bevölkerungsregister ausgewählt [49, 50]. Die Ziehung fand in zwei Schritten statt. Im ersten Schritt wurden alle 3 Großstädte (mit 17.076–65.977 Einwohnern), alle 12 Städte (mit 1.516–3.044 Einwohnern) und 17 von 97 Kleinstädten (mit weniger als 1500 Einwohnern) gezogen. Im zweiten Schritt wurden proportional zur Größe

jeder Gemeinde zufällig Individuen geschlechts- und altersstratifiziert ausgewählt. Nur Probanden mit deutscher Staatsbürgerschaft und Hauptwohnsitz in der Studienregion wurden berücksichtigt. In jeder 5 Jahres-Alters-Klasse befanden sich 292 Frauen und 292 Männer. Von den 7008 gezogenen Individuen schieden vor dem Studienstart 741 Personen aus, weil sie entweder gestorben oder aus der Studienregion ausgewandert waren. Von den verbliebenen 6267 Personen nahmen zwischen 1997 und 2001 4.308 Individuen an Baseline-SHIP teil (Teilnehmerquote 68,8%). Zwischen 2002 und 2006 wurden alle Probanden zu einem Untersuchungs-Follow-Up eingeladen. Von den 4308 zur Baseline untersuchten Probanden nahmen 3300 an dem Follow-Up teil (83,5 % von allen lebenden Probanden).

Seit Studienbeginn werden jährlich Informationen zu dem Vitalstatus der Probanden gesammelt. In dieser Arbeit wurden Mortalitätsdaten zum Stichtag 31. August 2007 verwendet. Probanden wurden zensiert, wenn sie verstorben sind oder deren aktueller Wohnort nicht mehr ermittelt werden konnte. Die Anzahl der Monate zwischen Erstuntersuchung und Austritt aus der Kohorte wurde als Beobachtungszeit definiert. Die mediane Beobachtungszeit betrug 8,5 Jahre (25^{te} Perzentile: 7,8 Jahre; 75^{te} Perzentile: 9,2 Jahre). Während der 13.913 Personenjahre verstarben 299 Probanden (217 Männer). Todeszertifikate wurden von den Gesundheitsämtern des Todesortes angefordert und die Todesursachen von einem zertifizierten Nosologen mittels des „International Classification of Diseases“ (ICD) kodiert. Danach wurden diese Kodierungen von zwei Internisten unabhängig voneinander validiert. Falls die beiden Internisten zu keinem übereinstimmenden Ergebnis gelangten, so wurde zusammen mit einem dritten Internisten eine Entscheidung gefällt.

2.2 Messung der verwendeten Variablen

2.2.1 Schilddrüsenparameter

Zur Baseline und zum Follow-Up der Studie wurde die Schilddrüsensonographie mit einer linearen 5-MHz-Sonde durchgeführt (VST-Gateway, Diasonics, Sancta Clara, USA). Das Schilddrüsenvolumen wurde durch das Produkt Länge x Breite x Tiefe x 0,479 [ml] errechnet [51]. Intra- und Interuntersuchervariabilitäten wurden vor Beginn der Studie und danach in halbjährlichen Abständen kontrolliert. Bei diesen Zertifizierungen haben sämtliche Untersucher die vorgegebenen Qualitätskriterien erfüllt: Der mittlere Abstand der Messungen eines Untersuchers sowie der Messungen zwischen zwei Untersuchern durfte 5% nicht überschreiten. Ebenfalls durfte die doppelte Standardabweichung nicht mehr als 25% von diesem Mittel abweichen. Schilddrüsenprogression wurde als Differenz zwischen den

Schilddrüsenvolumina von Follow-Up und Baseline berechnet. Struma wurde definiert als Schilddrüsenvolumen > 18 ml bei Frauen und > 25 ml bei Männern.

Blutproben der Probanden wurden in liegender Position genommen und in einem zentralen Labor analysiert. Serum-TSH-Spiegel wurden mittels eines Immunochemiluminiszenz-Assays analysiert (LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Deutschland). Die funktionelle Sensitivität des TSH-Assays betrug 0.03 mIU/L. Der Referenzbereich für Serum-TSH in der Studienregion wurde anhand der SHIP-Daten etabliert und beträgt 0,25 – 2,12 mIU/L [52]. Erniedrigtes TSH wurde definiert als Serum-TSH < 0,25 mIU/L. FT3 und FT4 wurden ebenfalls mittels eines Immunochemiluminiszenz-Assays analysiert (FT3: LUMItest, Brahms, Berlin, Deutschland; FT4: LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Deutschland). Subklinische Hyperthyreose wurde definiert als TSH < 0,25 mIU/L und FT3 und FT4 im Referenzbereich (FT3 ≤ 7,0 pmol/L und FT4 ≤ 18,9 pmol/L) [52].

Von jedem Probanden wurde im nicht-nüchternen Zustand eine Urinprobe entnommen. Aus diesen Urinproben wurde durch ein photometrisches Verfahren (Photometer ECOM 6122, Eppendorf, Hamburg, Germany) Jodid bestimmt [53]. Kreatinin wurde auf Basis der Jaffe-Reaktion bestimmt [54] und die Jodid-Kreatinin-Ratio wurde berechnet.

2.2.2 Weitere verwendete Variablen

Nach einer fünfminütigen Ruhepause wurden bei jedem Probanden systolischer und diastolischer Blutdruck in sitzender Position mittels eines Blutdruckmessgerätes mit digitaler Anzeige (HEM 705-CP, Omron Corporation, Tokyo, Japan) gemessen. In dreiminütigen Abständen wurde daraufhin weitere zwei Mal der Blutdruck bestimmt. Der Mittelwert aus zweiter und dritter Messung wurde in dieser Arbeit verwendet. Ein systolischer Blutdruck > 140 mmHg bzw. ein diastolischer Blutdruck > 90 mmHg wurden als erhöht betrachtet. Die Blutdruckamplitude wurde als Differenz zwischen systolischem und diastolischem Blutdruck definiert. Eine Blutdruckamplitude wurde als erhöht erachtet, wenn sie größer als die 75te Perzentile der Blutdruckamplitudenverteilung war. Ein Proband wurde als arteriell hypertensiv klassifiziert, wenn eine der folgenden drei Eigenschaften zutraf: systolischer Blutdruck > 140 mmHg, diastolischer Blutdruck > 90 mmHg oder Einnahme von Antihypertensiva.

Sozio-demographische Charakteristika, Historie von Erkrankungen (Herzinfarkt, Schlaganfall, Diabetes, bekannte Schilddrüsenerkrankungen) und Einnahme von

Medikamenten wurden in persönlichen Interviews erfragt. Bezüglich ihres Rauchverhaltens wurden die Probanden in 5 Gruppen unterteilt:

1. lebenslange Nichtraucher
2. Raucher zu beiden Zeitpunkten der Studie
3. Raucher zum Follow-Up, aber nicht zur Baseline
4. Raucher zur Baseline, aber nicht zum Follow-Up
5. Nichtraucher zu beiden Zeitpunkten der Studie, aber ehemalige Raucher

Ehemalige Raucher waren Individuen, die schon mal in ihrem Leben geraucht hatten, aber nicht innerhalb der letzten 12 Monate vor der Baseline-Untersuchung. Des Weiteren wurden für ehemalige und aktuelle Raucher Packyears berechnet. Dabei wurde die Dauer des Tabakkonsums in Jahren mit der Anzahl der Schachteln, die eine Person an einem Tag geraucht hat, multipliziert. 20 Zigaretten wurden als eine Schachtel definiert. Diese Einteilung wurde für das Manuskript zur Untersuchung der Assoziation zwischen Rauchverhalten und Struma verwendet. In den anderen beiden Arbeiten wurden Probanden hinsichtlich ihres Rauchstatus in 3 Gruppen kategorisiert (aktueller, ehemaliger oder Nicht-Raucher). Schilddrüsenmedikation wurde mittels des Anatomisch-therapeutischen-Klassifikations-Codes definiert (H03). Größe und Gewicht wurden mittels geeichter Geräte (Soehnle-Waagen GmbH, Nassau, Deutschland) gemessen und der Body Mass Index (BMI) berechnet: BMI = Gewicht (kg)/ Größe^2 (m^2).

2.2.3 Statistische Methoden

Zur Darstellung der Studienpopulationen wurde in jeder der drei Fragestellungen zunächst mit deskriptiven Statistiken gearbeitet. In der Arbeit zur Assoziation zwischen Rauchstatus und Struma wurde die Studienpopulation in drei Gruppen aufgeteilt (1. keine Struma Baseline und Follow-Up, 2. Struma zur Baseline, 3 Struma nur beim Follow-Up). In den anderen beiden Arbeiten wurden Probanden basierend auf Vorhandensein oder Nichtvorhandensein einer subklinischen Hyperthyreose in zwei Gruppen aufgeteilt. Innerhalb der jeweiligen Gruppen wurden nominal skalierte Variablen mittels totaler Anzahl und Anteil in % sowie stetige Variablen mittels Median und Interquartilabstand beschrieben. Für nominal skalierte Variablen wurden Gruppenvergleiche mittels eines Chi-Quadrat-Tests und für stetige Variablen mittels eines Wilcoxon Tests durchgeführt. Verbundene Stichproben wurden mittels des Vorzeichentests getestet.

Multivariable Regressionsanalysen wurden verwendet, um Expositionsvariablen mit abhängigen Variablen zu assoziieren. In der Arbeit zur Assoziation zwischen Rauchstatus und

Struma wurden logistische (inzidente Struma) und lineare Regressionen (Schilddrüsenwachstum) adjustiert für Alter, Geschlecht und BMI verwendet. In der Arbeit zur Assoziation zwischen subklinischer Hyperthyreose und Hypertonie wurden Poisson-Regressionen (dichotome abhängige Variablen) und Kovarianzanalysen (stetige abhängige Variablen) durchgeführt, die für Alter, Geschlecht, BMI, Rauchstatus und Zeit zwischen Baseline und Follow-Up-Untersuchung adjustiert wurden. In der Arbeit zur Assoziation zwischen erniedrigtem TSH und Mortalität wurden Cox-Regressionen benutzt. Hier wurden 3 unterschiedliche Modelle gerechnet; das erste unadjustiert, das zweite adjustiert für Alter und Geschlecht und das dritte zusätzlich adjustiert für Rauchstatus, Hypertonie, Schlaganfall, Myokardinfarkt, Diabetes mellitus Typ II, BMI, Cholesterol- und Fibrinogen-Spiegel. In allen Berechnungen wurde ein $p < 0.05$ als signifikant angesehen. Die Datenanalysen wurden mit SAS 9.1 (SAS Institute, Inc., Cary, NC, USA) durchgeführt.

3. Resultate

3.1 Der Einfluss des Rauchens auf die Entwicklung von Struma

Die 5-Jahres-Inzidenz für Struma betrug 17,7 %. Die mediane Iodid-Kreatinin-Ratio sank signifikant von 133,9 µg/g (99,8; 179,8 µg/g) zur Baseline auf 128,1 µg/g (89,9; 178,3 µg/g) zum Follow-Up ($p<0,001$). Probanden älter als 60 Jahre, die zu beiden Zeitpunkten der Studie angaben Raucher zu sein, hatten ein höheres Schilddrüsenwachstum verglichen mit jenen Probanden älter als 60 Jahre, die noch nie in ihrem Leben geraucht hatten ($\beta = 3,37$; 95%-Konfidenz-Intervall (KI): 0,84 – 5,89; $p<0,05$). Schloss man jene Probanden aus, die eine Struma zur Baseline aufwiesen, bestand keine signifikante Assoziation mehr zwischen Rauchen und Schilddrüsenwachstum ($\beta = 1,64$; 95%-KI: -1,20 – 4,48; $p=0,256$). In den anderen Altersgruppen gab es keine signifikanten Zusammenhänge zwischen Rauchstatus und Schilddrüsenwachstum. Bezüglich inzidenter Struma konnte eine signifikante inverse Assoziation zwischen Rauchverhalten und inzidenter Struma in der Gruppe der Probanden jünger als 40 Jahre gezeigt werden. In dieser Gruppe hatten Probanden, die zu beiden Zeitpunkten der Studie geraucht hatten, ein geringeres Risiko Struma zu entwickeln, als jene Probanden, die noch nie in ihrem Leben geraucht hatten (Odds-Ratio = 0,33; 95%-KI: 0,15 – 0,71). Um die Menge der gerauchten Zigaretten zu berücksichtigen, wurden Packyears mit Schilddrüsenwachstum assoziiert. Bei diesen Analysen zeigte sich ein signifikanter inverser Zusammenhang zwischen Packyears und Schilddrüsenwachstum bei Probanden jünger als 40 Jahren ($\beta = -1,82$; 95%-KI: -2,16 – -0,96; $p<0,001$).

3.2 Zusammenhang zwischen subklinischer Hyperthyreose und inzidenter arterieller Hypertonie in einer populationsbasierten Kohortenstudie

7,0 % aller Probanden wiesen zur Baseline eine subklinische Hyperthyreose auf. 286 Probanden entwickelten zum Follow-Up eine arterielle Hypertonie (5-Jahres-Inzidenz: 19,9 %). Der mediane systolische Blutdruck sank von 134 mmHg (121; 148 mmHg) zur Baseline auf 131 mmHg (118; 144 mmHg) zum Follow-up ($p<0,001$). Ebenfalls sank der diastolische Blutdruck von 83 mmHg (76; 90 mmHg) zur Baseline auf 80 mmHg (74; 88 mmHg) zum Follow-Up ($p<0,001$).

Multivariable Regressionsanalysen zeigten keine signifikanten Assoziationen zwischen subklinischer Hyperthyreose und inzidenter Hypertonie sowie weiteren Blutdruckvariablen (systolischer Blutdruck, diastolischer Blutdruck und Blutdruckamplitude). Des Weiteren konnten auch nach Ausschluss von Probanden mit diagnostizierter Schilddrüsenerkrankung, Schilddrüsenmedikation oder Antihypertensiva keine signifikanten Assoziationen nachgewiesen werden. Auch das Herabsetzen des unteren Serum-TSH-Grenzwertes auf 0.1 mIU/L führte zu keinen substantiellen Änderungen in den Ergebnissen. Um abschätzen zu können, in wie fern Probanden, die nicht am Follow-Up teilgenommen haben, die Ergebnisse beeinflusst haben, wurden alle Analysen unter Berücksichtigung von Drop-Out-Gewichten wiederholt. Bei diesen Analysen wurden jene Probanden stärker gewichtet, in dessen geschlechts- und altersspezifischen Gruppen mehr Probanden aus der Kohorte ausgeschieden sind. Bis auf eine Ausnahme zeigten sich auch hier keine signifikanten Assoziationen: In der Gesamtpopulation hatten Probanden mit subklinischer Hyperthyreose verglichen mit euthyreoten Probanden einen höheren diastolischen Blutdruck zum Follow-Up (β = 1,49 mmHg; 95%-KI: 0,22 – 2,75 mmHg; $p<0,05$). Allerdings bestand dieser Zusammenhang nicht mehr nach Ausschluss von Probanden mit Schilddrüsenmedikation oder einer diagnostizierten Schilddrüsenerkrankung (β = 1,32 mmHg; 95%-KI: -0,40 – 3,40 mmHg; $p=0,131$).

3.3 Zusammenhang zwischen erniedrigtem Thyreoidea-stimulierendes Hormon (TSH) und Mortalität

Bis zum 31.08.2007 starben 299 Probanden der SHIP-Studie. Im unadjustierten Modell war erniedrigtes TSH signifikant mit Mortalität assoziiert (Hazard Ratio: 1,69; 95%-KI: 1,19; 2,40, $p<0,05$). Nach Adjustierung für Alter und Geschlecht konnte dieser Effekt nicht mehr nachgewiesen werden (Hazard Ratio: 0,95; 95%-KI: 0,67; 1,36, $p>0,05$). Weitere

Adjustierung für Rauchstatus, Hypertonie, Schlaganfall, Myokardinfarkt, Diabetes mellitus Typ II, BMI, Cholesterol- und Fibrinogen-Spiegel führte zu keinen substantiell abweichenden Ergebnissen. Auch die Verwendung von alternativen Grenzwerten zur Definition von erniedrigtem TSH führte zu keinen signifikanten Änderungen in den Resultaten. Ebenfalls deckten geschlechtsstratifizierte Analysen keine signifikanten Assoziationen zwischen erniedrigtem TSH und Mortalität auf.

Auch zeigten sich im voll adjustierten Modell keine Assoziationen zwischen erniedrigtem TSH und Krebs- (Hazard Ratio: 1,05; 95%-KI: 0,67; 1,63, p=0,846) oder kardiovaskulärer Mortalität (Hazard Ratio: 1,08; 95%-KI: 0,61; 1,91, p=0,803). Auch hier führte die Anwendung alternativer Grenzwerte für Serum-TSH zu keinen wesentlich abweichenden Ergebnissen.

Zuletzt wurden Probanden mit erniedrigtem TSH in subklinische und manifeste Fälle unterteilt. Hier zeigten sich ebenfalls keine Zusammenhänge zwischen subklinischer bzw. manifester Hyperthyreose und Gesamt-, Krebs-, oder kardiovaskulärer Mortalität.

4. Diskussion

4.1 Der Einfluss des Rauchens auf die Entwicklung von Struma

Die Ergebnisse sprechen dafür, dass die Assoziation zwischen Rauchen und inzidenter Struma vom Alter abhängig ist. In SHIP konnte ein inverser Zusammenhang zwischen Rauchen und inzidenter Struma bei Personen jünger als 40 Jahren nachgewiesen werden, wohingegen bei Individuen älter als 60 Jahre ein positiver Zusammenhang zwischen Rauchen und Schilddrüsenprogression gezeigt werden konnte. Bisher durchgeführte Studien zu diesem Thema weisen darauf hin, dass die Assoziation von Rauchen und Struma stark von der Jodversorgung abhängt. So konnten die meisten Querschnittsanalysen aus Regionen mit aktuellem oder vorherigem Jodmangel [7, 8, 10, 55] einen positiven Zusammenhang zwischen Rauchen und prävalenter Struma nachweisen, so auch in Baseline-SHIP [2]. Weitere Studien aus Jodmangelgebieten [11, 56, 57] haben einen solchen Zusammenhang nicht nachweisen können, allerdings wurden in diesen Analysen wichtige Confounder wie z.B. Alter nicht berücksichtigt.

Querschnittstudien aus Regionen mit ausreichender Jodversorgung wiesen keinen Zusammenhang zwischen Rauchen und Struma nach [14, 15]. Dieses verstärkt die Hypothese, dass der Zusammenhang zwischen Rauchen und Struma stark abhängig von der Jodversorgung in der Studienregion ist [1]. In unseren Analysen konnte ein positiver Zusammenhang zwischen Rauchen und Schilddrüsenprogression bei Probanden älter als 60 Jahre nachgewiesen werden. Allerdings konnte dieser Effekt nach Ausschluss von Probanden mit Struma in Baseline-SHIP nicht mehr nachgewiesen werden. Dies bedeutet, dass nur jene Raucher ein erhöhtes Risiko für Schilddrüsenwachstum haben, die älter als 60 Jahre sind und bereits unter Struma litten.

Die Assoziation zwischen Rauchen und Struma kann durch erhöhte Konzentrationen von Cyanaten bei Rauchern erklärt werden [58]. Univalente Anionen mit gleicher Größe wie Iodid, so z.B. Cyanate, haben die Fähigkeit den Transport des Iodids in die Schilddrüse kompetitiv zu hemmen. Die Resultate aus SHIP unterstützen die Annahme, dass durch höhere Konzentrationen von Cyanaten die Entwicklung von Struma bei Rauchern in Jodmangelgebieten begünstigt wird, wohingegen Raucher in Regionen mit genügend Jodversorgung nicht so stark davon betroffen sind [59].

4.2 Zusammenhang zwischen subklinischer Hyperthyreose und inzidenter arterieller Hypertonie in einer populationsbasierten Kohortenstudie

In SHIP besteht kein Zusammenhang zwischen einer subklinischer Hyperthyreose und der Progression von arterieller Hypertonie und anderen blutdruck-spezifischen Endpunkten. Diese Ergebnisse stimmen mit jenen aus Baseline-SHIP überein [25]. Ebenfalls wurden in zwei asiatischen Studien [23, 24] und einer norwegischen Studie [22] keine Zusammenhänge zwischen subklinischer Hyperthyreose und arterieller Hypertonie nachgewiesen. Japan und Deutschland unterscheiden sich stark hinsichtlich ihrer Jodversorgung. Während Deutschland jahrzehntelang einen Jodmangel aufwies [4], besteht in Japan eher ein Jodüberschuss [60]. Des Weiteren ist die Prävalenz von arterieller Hypertonie in Japan signifikant höher als in Deutschland [61]. Der Fakt, dass Studien aus Regionen mit unterschiedlicher Jodversorgung und Prävalenz von arterieller Hypertonie zu dem gleichen Resultat kommen, unterstützt die Hypothese, dass kein Zusammenhang zwischen subklinischer Hyperthyreose und arterieller Hypertonie besteht.

Im Gegensatz zu unseren Ergebnissen konnte in der Busselton Studie, die in Australien durchgeführt wurde, ein positiver Zusammenhang zwischen subklinischer Hyperthyreose und Hypertonie nachgewiesen werden [26]. An dieser Studie nahmen 3940 Probanden ohne diagnostizierte Schilddrüsenerkrankung teil, wovon 2033 Teilnehmer eine subklinische Hyperthyreose aufwiesen. Allerdings wurden in dieser Studie nur bei ungefähr 50% der Teilnehmer Blutproben genommen, so dass nicht ausgeschlossen werden kann, dass ein Selektionsbias für die unterschiedlichen Ergebnisse zwischen der Busselton Studie und SHIP verantwortlich ist.

4.3 Zusammenhang zwischen erniedrigtem Thyreoidea-stimulierendes Hormon (TSH) und Mortalität

In SHIP konnte kein Zusammenhang zwischen erniedrigten Serum-TSH Spiegeln und Gesamt-, Krebs- oder kardiovaskulärer Mortalität nachgewiesen werden. Bezüglich Gesamtmortalität stimmen unsere Ergebnisse mit denen von zwei Studien überein [35, 39]. Allerdings konnten zwei weitere Studien [30, 34] einen Zusammenhang zwischen erniedrigten Serum-TSH-Spiegeln und Gesamt-Mortalität zeigen. Bezüglich subklinischer Hyperthyreose als Exposition korrespondieren unsere Ergebnisse mit jenen von vier anderen Studien [21, 32, 38, 41] und drei Meta Analysen [33, 37]. Lediglich zwei Studien [36, 42] und eine Meta Analyse [31] zeigten einen Zusammenhang zwischen einer subklinischen Hyperthyreose und Gesamt-Mortalität.

Die unterschiedlichen Ergebnisse der Meta-Analysen könnten darauf zurückzuführen sein, dass Ergebnisse der Studie von Parle et al. [35] unterschiedlich Berücksichtigung fanden. In dieser Studie [35] wurden erniedrigte Serum TSH Spiegel mit Mortalität zu fünf unterschiedlichen Follow-Up-Zeiten assoziiert (2, 3, 4, 5 und 10 Jahre). Für das 10-Jahres-Follow-Up konnte kein signifikanter Zusammenhang gezeigt werden, allerdings für sämtliche kürzere Follow-Up Zeiten (2, 3, 4 und 5 Jahre). Die Meta-Analyse von Haentjens et al. [31] verwendete die Ergebnisse des 5-Jahres-Follow-Ups, wohingegen die anderen Meta-Analysen [33, 40] auf die Ergebnisse des 10-Jahres-Follow-Ups zurückgegriffen haben.

Ein weiterer Grund für die kontroversen Resultate der Meta-Analysen könnte in der Anzahl der betrachteten Studien begründet liegen. So verwendete Haentjens et al. [31] sieben Studien, Ochs et al. [33] fünf, Singh et al. [37] drei und Völzke et al. [40] zwei. Zum Teil kann aber die Vergleichbarkeit zwischen den Original-Studien nicht garantiert werden, da die Original-Studien sich hinsichtlich Wahl der Confounder, Beobachtungszeiten, Definition von subklinischer Hyperthyreose und Art der betrachteten Population unterscheiden. Aus diesem Grund sollte man genau prüfen, welche der Original-Studien man in eine Meta Analyse aufnimmt. So haben allein vier der in der Meta-Analyse von Haentjens et al. [31] betrachteten Studien [30, 35, 36, 62] nicht für wichtige Confounder wie Alter und Rauchstatus adjustiert. In unserer Analyse konnte man einen positiven Zusammenhang zwischen erniedrigtem Serum-TSH und Gesamt-Mortalität sehen, wenn man nicht für Alter adjustiert hatte. Aus diesem Grund ist es wichtig für relevante Confounder zu adjustieren, da man sonst zu falschen Ergebnissen gelangen könnte.

Ferner wurde in den Original-Studien subklinische Hyperthyreose unterschiedlich definiert. In den meisten Fällen schwankte der untere Grenzwert für Serum-TSH zwischen 0.3 mIU/L [30] und 0.5 mIU/L [35]. Die meisten dieser Studien betrachteten dabei FT4 [21, 32, 34, 36, 38, 39, 41] zur Definition von subklinischer Hyperthyreose, wohingegen andere Studien dies nicht taten [30, 35]. Ebenfalls könnten Unterschiede in der Beobachtungszeit zu diskrepanten Ergebnissen geführt haben. Kurze Beobachtungszeiten sind problematisch, weil der Einfluss der Exposition auf die Erkrankung zu schwach sein könnte. Auf der anderen Seite sind aber auch lange Beobachtungszeiten von Nachteil, weil sich der Expositionsstatus der Probanden nach der Baseline-Untersuchung verändern kann und man somit den Einfluss der Expositionsvariable auf die Erkrankung unterschätzen könnte.

Hinsichtlich kardiovaskulärer Mortalität stimmen unsere Ergebnisse mit den meisten anderen Studien [21, 34, 35, 41] und Meta-Analysen [33, 37, 40] überein. Im Gegensatz dazu fanden zwei

Studien einen positiven Zusammenhang zwischen subklinischer Hyperthyreose und kardiovaskulärer Mortalität [30, 32], wobei die Studie von Iervasi et al. [32] nicht mit unserer Studie vergleichbar ist, da in dieser Studie nur Patienten mit Herzerkrankung betrachtet worden sind.

Eine wesentliche Limitation unserer Studie besteht darin, dass die Probanden zu Baseline über ihre Schilddrüsenfunktionswerte unterrichtet worden sind. Auf Basis dessen ist es möglich, dass sie sich in Therapie begeben haben, um ihre Schilddrüsenüberfunktion auszugleichen. In SHIP gibt es keine Daten, die belegen, ob ein Proband sich direkt nach der Baseline-Untersuchung in Therapie begeben hat. Dieses könnte dazu geführt haben, dass der Einfluss von einer subklinischen Hyperthyreose in Hinblick auf die Mortalität unterschätzt wurde. Eine weitere Limitation unserer Studie ist die Größe der Studienpopulation. Auch wenn das Hazard Ratio meistens nahe bei 1 war, können wir nicht ausschließen, dass wir eventuell sehr schwache Assoziationen aus Gründen der statistischen Power übersehen haben. Insbesondere bei den Analysen hinsichtlich manifester Hyperthyreose und Krebs-Mortalität waren die Fallzahlen gering. Darüber hinaus wurden die Blutabnahmen in SHIP nicht zu festen Zeiten, sondern über den ganzen Tag verteilt zwischen 07.00 und 16.00 Uhr, durchgeführt. In der Literatur gibt es Hinweise darauf, dass Serum-TSH einem zirkadischen Rhythmus folgt [63]. Aus diesem Grunde haben wir Analysen stratifiziert nach Blutabnahmezeitpunkt (vor und nach 12.00 Uhr) durchgeführt, die aber keine substantiell anderen Ergebnisse gezeigt haben.

5. Zusammenfassung

Während kein Zweifel darüber besteht, dass manifeste Schilddrüsenerkrankungen signifikante Effekte auf das Herz-Kreislauf-System aufweisen, ist die Evidenzlage bezüglich der Assoziationen von subklinischen Schilddrüsenauffälligkeiten mit kardiovaskulären Risikofaktoren und Erkrankungen weitaus weniger konsistent. Aus diesem Grunde habe ich mich in meiner Dissertation mit dem Zusammenhang von subklinischen Schilddrüsenauffälligkeiten und Mortalität bzw. der Entwicklung von Bluthochdruck innerhalb der „Study of Health in Pomerania“ (SHIP) beschäftigt. SHIP ist eine große Bevölkerungsstudie in Ostvorpommern. Zwischen 1997 und 2001 nahmen 4308 Probanden an der Erstuntersuchung teil. Zwischen 2002 und 2006 haben davon 3300 Probanden an einem Untersuchungs-Follow-Up teilgenommen. Meine Analysen haben gezeigt, dass kein Zusammenhang zwischen einer subklinischen Schilddrüsenüberfunktion und der Entwicklung von Bluthochdruck zwischen Erstuntersuchung und Follow-Up-Untersuchung besteht. Ebenfalls konnte ich nicht zeigen, dass eine Assoziation zwischen einer subklinischen Schilddrüsenüberfunktion und Mortalität besteht. Diese Ergebnisse sind wichtig, da sie ein Indiz darauf geben, ob Menschen mit subklinischen Schilddrüsenauffälligkeiten therapiert werden sollten oder nicht.

Der zweite Teil meiner Dissertation beschäftigt sich mit der Jodversorgung in Ostvorpommern. Ostvorpommern war bis Anfang der 1990er ein Jodmangelgebiet. In den 1990ern wurde dieser Jodmangel durch Hinzugabe von jodiertem Salz zur Nahrungsproduktion ausgeglichen. Wegen dem lange vorherrschenden Jodmangel haben viele Menschen in Ostvorpommern eine Struma (Schilddrüsenvergrößerung). Die Struma-Prävalenz betrug zur Erstuntersuchung in SHIP 36.1 %. In meiner Analyse habe ich untersucht, inwiefern der Rauchstatus sich auf die Entwicklung einer Struma zwischen Erstuntersuchung und Follow-Up-Untersuchung ausgewirkt hat. Aus der Literatur ist bekannt, dass Raucher in Jodmangelgebieten eher eine Struma entwickeln als Raucher in Gebieten mit ausreichender Jodversorgung. Da ich keinen Zusammenhang zwischen Rauchen und der Entwicklung einer Struma zeigen konnte, spricht dies für eine derzeitig ausreichende Jodversorgung der Bevölkerung in Ostvorpommern.

6. Literatur

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7. Anhang

7.1. Eidesstattliche Erklärung

Hiermit erkläre ich, daß ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät vorgelegt worden.

Ich erkläre, daß ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

7.2. Danksagung

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7.3. Verwendete Zeitschriftenartikel

Die dieser kumulativen Arbeit zugrundeliegenden wissenschaftlichen Artikel sind nachfolgend aufgelistet. Die Artikel sind auf den nachfolgenden Seiten reproduziert. Die Sortierung entspricht der inhaltlichen Reihenfolge.

1 **Ittermann, T**., Schmidt, C. O., Kramer, A., Below, H., John, U., Thamm, M., Wallaschofski, H. and Volzke, H., Smoking as a risk factor for thyroid volume progression and incident goiter in a region with improved iodine supply, European journal of endocrinology / European Federation of Endocrine Societies, 2008, 159: 761-766.

2 Volzke, H., **Ittermann, T.**, Schmidt, C. O., Dorr, M., John, U., Wallaschofski, H., Stricker, B. H., Felix, S. B. and Rettig, R., Subclinical hyperthyroidism and blood pressure in a population-based prospective cohort study, European journal of endocrinology / European Federation of Endocrine Societies, 2009, 161: 615-621.

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CLINICAL STUDY

Smoking as a risk factor for thyroid volume progression and incident goiter in a region with improved iodine supply

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Abstract

Objective: The role of smoking in the pathogenesis of thyroid enlargement is currently under debate. It has been hypothesized that the effect of smoking on increased thyroid volume is larger in regions with than in regions without iodine deficiency. The aim of this paper was to investigate the association of smoking with thyroid volume progression and incident goiter for different age-strata in a region with improved iodine supply.

Design and methods: The population-based Study of Health in Pomerania compromised 3300 subjects with complete 5-year examination follow-up. Data from 2484 participants without known history of thyroid disorder or thyroid medication were analyzed. Thyroid size was evaluated by ultrasound. Determinants of thyroid volume progression and incident goiter, i.e., newly occurred goiter between baseline and follow-up, were analyzed by linear and logistic regression respectively.

Results: Participants aged 20–39 years who were current smokers at baseline and at follow-up had a lower risk of incident goiter (odds ratio: 0.33; 95% confidence interval (CI): 0.15; 0.71; $P=0.005$). In this subpopulation, age was inversely related to thyroid volume progression. In subjects aged 60–79 years, smoking at baseline and follow-up was a risk factor for thyroid volume progression (β: 3.37; 95% CI: 0.84; 5.89; $P=0.009$). After exclusion of individuals who had actual goiter in ultrasound at baseline, this association disappeared.

Conclusion: We conclude that the inverse association between smoking and goiter in young adults and the lacking association of smoking with goiter and thyroid volume progression in adult non-goitrous subjects indicate that smoking has a declining impact on thyroid growth in the study region. Our findings mirror the improved iodine supply of Northeast Germany.

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Introduction

The role of smoking in the pathogenesis of thyroid enlargement is currently under debate. It has been hypothesized that the effect of smoking on increased thyroid volume is larger in regions with than in regions without iodine deficiency (1–4). Previous studies (5, 6), which have been conducted in iodine-deficient areas, detected smoking as a risk factor for thyroid enlargement. Other studies (7), however, did not confirm this finding. Evidence from regions with sufficient iodine supply is likewise conflicting. Some studies (8, 9) detected an association between smoking and thyroid enlargement, while others (10, 11) did not. Additionally, a twin study that recruited participants from regions with and without sufficient iodine supply detected smoking as a risk factor for goiter (12). Most of the previous studies are limited by their cross-sectional (1, 4–12) or retrospective design (13). Methodical constraints, such as selection or recall bias, might have additionally impaired results. Only one study (3) used a prospective cohort design, but was conducted in a selected population of parous women. Therefore, we sought to investigate the association between smoking and thyroid growth in a population-based prospective cohort study.

The improved supply of iodine salt into food productions and individual salt consumption during the 1990s in the study region of Northeast Germany led us to the paradoxical situation of high goiter prevalence in a region of improved iodine supply (14). Previous studies (15) investigated the difference in thyroid growth between regions of mild and moderate iodine deficiency in different age strata. Especially, younger subjects should show more benefit from iodine improvement than elder subjects. Therefore, we investigated the association of smoking with thyroid volume progression and incident goiter in different age strata.

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Materials and methods

Study subjects

The Study of Health in Pomerania (SHIP) is a population-based study in West Pomerania, a region in the north-east of Germany including the three cities Greifswald, Stralsund, Anklam, and 29 surrounding communities (16). The total population comprised 212 157 inhabitants. As in most parts of Germany, West Pomerania is a region of former iodine deficiency (14), which resulted in a high prevalence of goiter (6). During the 1990s, improved iodine supplementation has normalized this deficiency level resulting in a median iodine excretion value of 124 μg/l (14). Currently, in the KiGGS study, a German survey in children and adolescents, a median iodine excretion of 117 μg/l was detected (17). SHIP and KiGGS argue for an improvement of iodine excretion levels in Germany on a lower recommended level.

For the SHIP baseline study, a sample from the population aged 20 to 79 years was drawn. Selection of the sample was done using population registries and performed in two steps. In Germany, all residents have to be registered. First, the three cities of the region (with 17 076–65 977 inhabitants) and 12 towns (with 1516–3044 inhabitants) were selected, and then 17 out of 97 smaller towns (with less than 1500 inhabitants) were drawn at random. Secondly, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community, and stratified by age and gender. Only individuals with German citizenship and main residency in the study region were included. Finally, 7008 subjects were sampled, with 292 persons of each gender in each of the twelve 5-year age strata. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects. Selected persons received a maximum of three written invitations. In case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The population of the baseline SHIP finally comprised 4310 participants (2117 men and 2193 women) corresponding to a final response of 68.8% (16). Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006, all participants were re-invited to take part in an examination follow-up, in which 3300 subjects took part (1589 men and 1711 women; 83.5% of all eligible subjects). The median follow-up time was 5.00 years (minimum, 4.42 years; maximum, 8.58 years; 17 314.7 person years). All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Among the participants, 77 (33 men and 44 women) had missing data in one or more of the variables involved in the data analysis, 717 (218 men and 499 women) had self-reported known thyroid disorders at baseline or follow-up, and 58 (14 men and 44 women) received thyroid therapy at baseline or follow-up. We excluded these 852 individuals (265 men and 587 women) from further analysis, resulting in a study population of 2448 (1324 men and 1124 women) participants. When using incident goiter as the dependent variable, we excluded a further 801 subjects (468 men and 333 women) with goiter at baseline. This resulted in a population of 1647 participants (856 men and 791 women).

Assessments

Socio-demographic characteristics, smoking, and history of known thyroid diseases or use of antithyroid medication were assessed by computer-aided personal interviews. According to cigarette smoking status, participants were categorized into five groups (1, never smoker; 2, smoker at both baseline and follow-up; 3, smoker at follow-up but not at baseline; 4, smoker at baseline but not at follow up; 5, nonsmoker at baseline and follow-up but former smoker). Former smokers were individuals who had smoked during their lifetime but not in the last 12 months prior to the time of the baseline examination. Pack years for current and former smokers were calculated by multiplying the duration of smoking in years with the amount of packs (20 cigarettes were defined as one pack) an individual smoked a day. Pack years were divided into three categories (1, 0 pack years; 2, # pack years $<$ median pack years of former and current smokers; 3, # pack years $>$ median pack years of former and current smokers). Height and weight were measured for the calculation of the body mass index: BMI = weight (kg)/height^2 (m^2).

Iodine concentrations were measured by urine iodine excretion. Spot urine samples of the participants were collected and analyzed for iodine and creatinine concentration by photometric procedure (Photometer ECOM 6122, Eppendorf, Hamburg, Germany) with Sandell and Kolthoff reaction (18). The iodine–creatinine ratio was calculated by dividing urinary iodine by urinary creatinine concentration.

Blood samples were analyzed in one central laboratory. Serum thyrotropin (TSH), free triiodothyronine (FT_3), and free thyroxine (FT_4) levels were determined by immunochemiluminescent procedures (FT_3, LUMItest, Brahms, Berlin, Germany; TSH and FT_4, LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany).

Thyroid ultrasonography was performed in both examinations with an Ultrasound VST-Gateway, with a 5 MHz linear array transducer (Diasonics, Santa Clara, CA, USA). The normal thyroid echo pattern was classified as homogeneous. A homogeneous echo pattern with reduced echogenicity was defined as hypoechogenic. Thyroid volume was calculated as length × width × depth × 0.479 (ml) for each lobe (19). The intra- and inter-observer reliabilities were assessed before the start of the study and afterwards semi-annually during the study.

All measurements of the thyroid volume showed Spearman correlation coefficients of >0.85 and mean differences (± 2 S.D.) of the mean bias of $<5\%$ ($<25\%$). Thyroid volume progression was defined as difference between thyroid size at follow-up and baseline. Goiter was defined as a thyroid volume >18 ml in women and >25 ml in men (20).

Statistical analysis

Data on quantitative characteristics are expressed as median and inter-quartile range. Data on qualitative characteristics are expressed as percent values or absolute numbers, as indicated. The study population was divided into three groups according to the presence or absence of goiter at baseline and follow-up (1, presence of goiter at baseline; 2, absence of goiter at baseline and follow-up; 3, absence of goiter at baseline but presence at follow-up). Comparisons between groups were made using χ^2 test (qualitative data) or Wilcoxon test (quantitative data). Wilcoxon's signed rank test was used for paired data. Determinants of thyroid volume change and incident goiter were analyzed by linear and logistic regression respectively. All models were adjusted for age, gender, and body mass index. In the first step, both analyses were performed separately for three different age strata (20–39, 40–59, and 60–79 years). In the second step, analyses were performed for the whole population, and interactions between the smoking variables and age were tested. Interactions were kept in the models for P values <0.1. For all interactions, the β and its S.E.M. are outlined. From linear regression models, the β and its 95% confidence interval (95% CI) and from logistic regression, odds ratio, and its 95% CI are given. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Among the 1647 participants without goiter at baseline, 291 (151 men and 140 women) individuals developed goiter during follow-up (5-year incidence: 17.7%). Individuals who developed goiter during follow-up had lower serum TSH levels, were elder, more often overweight, less often current smokers but more often former smokers, and reported more pack years than subjects who had no goiter at baseline and follow-up (Table 1). Compared with subjects without goiter at both baseline and follow-up, individuals with goiter at baseline were elder, more often smokers, less often females, had a higher BMI and lower levels of serum TSH, but higher levels of FT_3. Current or former smokers with goiter at baseline had more pack years than smokers with no goiter at baseline and follow-up. Ever smokers at baseline had an improved risk of goiter compared with never smokers at baseline (relative risk: 1.15; 95% CI: 1.08, 1.21). In all three groups, iodine–creatinine ratio decreased during follow-up. In the whole selected population, the median iodine–creatinine ratio decreased from 133.9 μg/g (99.8 μg/g; 179.8 μg/g) at baseline to 128.1 μg/g (89.9 μg/g; 178.3 μg/g) at follow-up ($P<0.001$).

Table 2 shows the results of the age-specific linear regression with thyroid volume progression as outcome. Subjects who were smokers at baseline and follow-up in

Table 1 Characteristics of the study population with and without development of goiter.

	No goiter at baseline and follow-up ($n=1356$)	**Goiter at baseline** ($n=801$)	**Goiter at follow-up only** ($n=291$)	P^a	P^b
Age (baseline) (years)	45 (32; 57)	52 (41; 64)	53 (40; 64)	<0.001	<0.001
Thyroid volume (baseline) (ml)	14.84 (12.0; 18.0)	27.40 (22.7; 32.6)	17.81 (15.8; 22.4)	<0.001	<0.001
Thyroid volume (follow-up) (ml)	15.44 (12.5; 18.6)	26.65 (21.4; 34.4)	25.43 (19.9; 27.8)	<0.001	<0.001
Urinary iodine creatinine-ratio (baseline) (μg/g)	131.0 (98.2; 176.5)	138.2 (101.4; 186.8)	138.1 (101.9; 178.5)	0.216	0.106
Δ Urinary iodine–creatinine ratio (μg/g)	−3.6 (−58.8; 44.7)	−3.9 (−57.6; 38.9)	−2.9 (−57.8; 48.3)	0.543	0.788
Body mass index (baseline) (kg/m^2)	25.71 (22.9; 28.8)	27.68 (25.0; 30.7)	27.87 (24.7; 30.5)	<0.001	<0.001
Gender (men)	705 (52.0%)	468 (58.43%)	151 (51.9%)	0.004	0.975
Cigarette smoking					
Never smoker	555 (40.9%)	252 (31.46%)	120 (41.2%)	<0.001	<0.001
Smoker before baseline	416 (30.7%)	284 (35.46%)	113 (38.8%)		
Smoker at baseline only	73 (5.4%)	52 (6.49%)	17 (5.8%)		
Smoker at follow-up only	63 (4.7%)	24 (3.00%)	9 (3.1%)		
Smoker at baseline and follow-up	249 (18.4%)	189 (23.60%)	32 (11.0%)		
Pack years	11.1 (5.5; 23.8)	17.3 (9.4; 29.0)	15.0 (6.7; 28.1)	<0.001	0.019
Serum thyrotropin (baseline) (mU/l)	0.79 (0.57; 1.10)	0.53 (0.36; 0.76)	0.61 (0.42; 0.83)	<0.001	<0.001
Free triiodothyronine (baseline) (pmol/l)	5.26 (4.72; 5.78)	5.20 (4.70; 5.80)	5.24 (4.80; 5.80)	0.680	0.709
Free thyroxin (baseline) (pmol/l)	12.40 (10.80; 13.90)	12.70 (11.10; 14.36)	12.32 (10.58; 14.20)	0.005	0.996

Data are given as numbers (percentage) or median (25th and 75th percentile). Δ Change between baseline and follow-up.
[a]χ^2 test (qualitative data) and Wilcoxon test (quantitative data) for row one and two.
[b]χ^2 test (qualitative data) and Wilcoxon test (quantitative data) for row one and three.

Table 2 Risk factors for thyroid volume progression.

	20–39 years β (95% confidence interval)	**40–59 years** β (95% confidence interval)	**60–79 years** β (95% confidence interval)
Smoker at baseline and follow-up	−0.54 (−1.18; 0.08)	−0.46 (−1.42; 0.50)	3.37 (0.84; 5.89)*
Smoker at baseline only	0.12 (−0.88; 1.12)	0.48 (−1.06; 2.03)	−0.31 (−3.10; 2.47)
Smoker at follow-up only	−0.47 (−1.55; 0.62)	−0.75 (−2.61; 1.10)	−0.69 (−5.22; 3.83)
Smoker only before baseline	−0.25 (−0.93; 0.44)	0.62 (−0.20; 1.45)	0.93 (−0.43; 2.29)
Age (years)	−0.10 (−0.15; −0.05)*	0.01 (−0.05; 0.07)	0.03 (−0.06; 0.12)
Gender (ref. female)	0.34 (−0.18; 0.86)	−0.56 (−1.26; 0.14)	0.20 (−1.13; 1.52)
Body mass index (kg/m^2)	0.06 (−0.01; 0.12)	0.05 (−0.02; 0.12)	0.12 (−0.01; 0.26)

Linear regression for thyroid volume progression as outcome. Reference group for smokers: non-smokers. *$P<0.05$.

the elder subgroup (60–79 years) had a higher risk of thyroid volume progression than nonsmokers. However, after exclusion of individuals with goiter at baseline, this association disappeared (β: 1.64; 95% CI: −1.20, 4.48; $P=0.256$). An interaction between smoking and age ≥ 60 years was detected after including two dichotomous age variables (I, 4–59 vs <40 years; II, ≥ 60 vs <40 years) and their interaction terms with smoking into the model ($\beta=3.50$, S.E.M.$=0.97$, $P=0.001$).

Table 3 outlines the results of the logistic regression with incident goiter as outcome for the three age strata. In the population <40 years, smoking at baseline and follow-up was inversely associated with goiter. Considering one logistic model over the whole population revealed an interaction between age and smoking ($\beta=0.03$, S.E.M.$=0.02$, $P=0.055$). For clarifying this interaction, a logistic model with two dichotomous age variables (I, 40–59 vs <40 years; II, ≥ 60 vs <40 years) was performed. This calculation revealed significant interactions of smoking and age of 40–59 years ($\beta=1.10$, S.E.M.$=0.47$, $P=0.019$) and age of ≥ 60 years ($\beta=1.71$ S.E.M.$=0.70$, $P=0.014$) respectively.

For taking the lifetime amount of tobacco consumption into account, we repeated all analyses for pack years as exposition variable. Among the 2448 individuals, there were 308 former or current smokers (160 men and 148 women), for which pack years could not be calculated due to missing values. Thus, 2140 subjects (1164 men and 976 women) were available for analysis on the association between pack years and thyroid volume progression, and 1423 subjects (740 men and 683 women) for the association between pack years and goiter respectively. Linear regression revealed a significant inverse association between pack years and thyroid volume progression in subjects aged 20–39 years (β: −1.82; 95% CI: −2.16, −0.96, $P<0.001$). Other significant associations between lifetime amount of smoking and thyroid enlargement were not detected (data not shown).

Discussion

In the present study, we investigated the association of smoking with incident goiter and thyroid volume progression in a region of improved iodine supply. We detected age-dependent effects of smoking on the dependent variables. While there was an inverse association between smoking and goiter in younger subjects, a positive association was found between smoking and thyroid volume progression in older subjects.

West Pomerania is a region with former iodine deficiency. In the middle of the 1990s, the iodine supply was increased by means of iodized salt in food productions and individual salt consumption. This led to an increase in urinary iodine concentration (21) and to a decrease in goiter prevalence in adolescents living in the study region (22). Because sufficient iodine supply was only available for the past decade in West Pomerania, we observed the paradoxical situation of a high prevalence of goiter and other iodine deficiency-related disorders in a region of improved iodine supply (14). The results of the iodine monitoring in the KiGGS study (17) among children and adolescents demonstrated that Germany meanwhile has an improved

Table 3 Risk factors for incident goiter.

	20–39 years odds ratio (95% confidence interval)	**40–59 years odds ratio** (95% confidence interval)	**60–79 years odds ratio** (95% confidence interval)
Smoker at baseline and follow-up	0.33 (0.15; 0.71)*	1.17 (0.62; 2.21)	2.29 (0.67; 7.77)
Smoker at baseline only	1.03 (0.41; 2.57)	2.19 (0.89; 5.39)	0.49 (0.10; 2.33)
Smoker at follow-up only	0.57 (0.19; 1.74)	0.96 (0.31; 3.00)	0.68 (0.07; 6.30)
Smoker before baseline	0.88 (0.47; 1.64)	1.12 (0.69; 1.83)	1.41 (0.77; 2.58)
Age (years)	1.02 (0.97; 1.07)	1.00 (0.97; 1.04)	1.01 (0.97; 1.06)
Gender (ref. female)	0.73 (0.43; 1.23)	0.73 (0.48; 1.13)	1.09 (0.60; 1.99)
Body mass index (kg/m^2)	1.12 (1.06; 1.19)*	1.06 (1.02; 1.11)*	1.10 (1.04; 1.16)*

Logistic regression for the incidence of goiter as outcome. Reference group for smokers: non-smokers. *$P<0.05$.

iodine supply at a lower recommended level. The present analysis revealed similar results. Due to the large study population, the slight decrease in the iodine–creatinine ratio over time attained statistical significance. Iodine excretion at follow-up, however, was still on a lower recommended level.

Smoking was inversely related with goiter in subjects <40 years and positively associated with thyroid volume progression in subjects ≥ 60 years. Previous studies on the prevalence of goiter from formerly or currently iodine-deficient areas (1, 2, 5, 23) reported smoking as a risk factor for goiter whereas others did not (7, 24, 25). The fact that the latter studies (7, 24, 25) were only based on bivariate comparisons between smoking and goiter might have resulted in false conclusions because confounders (e.g. age) were not considered. Furthermore, our analysis that used lifetime amount of tobacco smoking as exposition variable confirmed the inverse association between increased amount of pack years and thyroid volume progression in the population <40 years. An association with goiter was not present in this subgroup. In the age group ≥ 60 years, no interaction between pack years and thyroid enlargement was detected, which argues for an absence of an association between lifetime amount of tobacco smoking and goiter at older ages.

In line with these results, other studies (10, 11) conducted in an iodine-replete region did not detect any association between smoking and thyroid enlargement. This endorses the hypothesis that the association between smoking and thyroid enlargement is present in regions of iodine deficiency rather than in areas with sufficient iodine supply (4). In our analysis, smoking was a risk factor for thyroid volume progression only in the population ≥ 60 years and, within this, only for those with goiter at baseline. After exclusion of these subjects, the association between smoking and thyroid change was no longer present. This finding suggests that individuals ≥ 60 years are only affected by thyroid volume progression, if they already have developed goiter during time of iodine deficiency.

The goitrogenous effect of cigarette smoking can be partly explained by elevated plasma cyanate (CN^-) concentrations in smokers (26). Univalent anions with sizes similar to iodide, such as CN^-, are able to competitively inhibit the transport of iodide into the thyroid gland. Our findings support the notion, that in regions with iodine deficiency this cohesion might fortify the development of goiter in smokers, whereas in regions with sufficient iodine supply smokers might be not that greatly affected (27).

In subjects <40 years, age was inversely associated with thyroid volume progression, but was not related to the risk of goiter. This finding supports the notion that, in general, younger individuals are less strongly affected by iodine deficiency than older individuals (14) and that this subpopulation particularly benefits from iodine fortification programs.

The definition of known thyroid disorders by self-report, which was used as exclusion criterion, was certainly one limitation of the present study. Due to the vague symptoms of most thyroid diseases, the participant might be self-reported healthy, but suffer from biochemical thyroid disease. Therefore, we cannot fully rule out a certain misclassification in the chosen exclusion criterion.

We conclude that the inverse association between smoking and goiter in young adults and the lacking association of smoking with goiter and thyroid volume progression in adult non-goitrous subjects indicate that smoking has a declining impact on thyroid growth in the study region. Our findings mirror the improved iodine supply of Northeast Germany.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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CLINICAL STUDY

Subclinical hyperthyroidism and blood pressure in a population-based prospective cohort study

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Abstract

Objectives: There is current controversy on the association between subclinical hyperthyroidism and hypertension. Data from cohort studies have not been available yet. The present study was designed to longitudinally investigate possible associations of subclinical hyperthyroidism with blood pressure, pulse pressure and the risk of hypertension.

Methods: We used data from the population-based, prospective cohort Study of Health in Pomerania and included 2910 subjects (1469 women) aged 20–79 years with completed 5-year examination follow-up. Subjects with increased serum TSH levels or overt hyperthyroidism were excluded. Serum TSH levels below 0.25 mIU/l with free triiodothyronine and free thyroxine levels within the reference range were defined as subclinical hyperthyroidism. Blood pressure was measured according to standard methods.

Results: Multivariable analyses adjusted for age, sex, overweight, obesity, smoking status and time between the examinations did not reveal any statistically significant association between subclinical hyperthyroidism and any of the blood pressure-related variables in the whole study population. Although the 5-year hypertension incidence was higher in subjects with subclinical hyperthyroidism compared with those without (31.4 vs 19.2%; risk ratio 1.64; 95% confidence interval (CI) 1.17–2.28, $P=0.006$), both groups did not differ with respect to the risk of hypertension, after analyses were adjusted for confounders (relative risk 1.23, 95% CI 0.91–1.68, $P=0.182$). Analyses yielded similar results in subjects without thyroid disease and in those who took no antihypertensive medication.

Conclusion: Subclinical hyperthyroidism is not associated with changes in blood pressure, pulse pressure or incident hypertension.

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Introduction

The role of subclinical hyperthyroidism in cardiovascular disorders is a matter of debate and subject to ongoing controversy. Several previous studies found associations of subclinical hyperthyroidism with cardiovascular disorders such as endothelial dysfunction (1), left ventricular hypertrophy (2), thickened artery walls (3) or atrial fibrillation (4). The cardiovascular disorders associated with subclinical hyperthyroidism may be a direct effect of thyroid hormone disturbance. Alternatively, they may reflect an increased arterial pressure level in subjects with subclinical hyperthyroidism.

In the past few years, several population-based studies (5–7) have investigated the association of subclinical hyperthyroidism with blood pressure and hypertension. One of these studies (5) demonstrated that subjects with subclinical hyperthyroidism had a 2.8-fold (95% confidence interval (CI) 1.3–6.0) increased risk of hypertension compared with euthyroid subjects. Other studies (6, 7), however, did not find such an association.

A common drawback of all previous studies on the association of thyroid function with blood pressure and hypertension (5–7) is their cross-sectional design, which makes them prone to false conclusions regarding the sequence of cause and effect. The demonstration of a longitudinal relation between subclinical hyperthyroidism and high blood pressure would be of high relevance for the ongoing discussion on whether subclinical hyperthyroidism should be treated and at what serum TSH level this treatment should be initiated (8, 9).

Therefore, the present study was designed to investigate whether subclinical hyperthyroidism

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is associated with increased blood pressure, pulse pressure and the risk of hypertension 5 years later. The study is based on data from a sample of a general adult population with prospective 5-year follow-up examinations.

Methods

Setting and study population

The Study of Health in Pomerania (SHIP) is a population-based study conducted in West Pomerania, the north-east area of Germany (10). The study region is a previously iodine-deficient area. Voluntary iodine fortification substantially added to a stable and adequate iodine supply in the study area since the middle of the 1990s (11).

For the baseline examinations, a sample of 6267 eligible subjects aged 20–79 years was drawn from population registries. Only individuals with German citizenship and main residency in the study area were included. Selected persons received a maximum of three written invitations. In the case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The SHIP population finally comprised 4310 participants (response 68.8%). The study was monitored by a review board of independent scientists. Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006, all participants were reinvited for an examination follow-up, in which 3300 subjects (83.5% of still living and achievable persons) took part (12, 13). All participants gave informed written consent. The study protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Among the 3300 participants, there were 106 subjects (65 women), who had missing values in one or more of the considered variables, and 284 participants (177 women) who had increased serum TSH levels or overt hyperthyroidism as defined by serum TSH levels below the lower reference range and free triiodothyronine (FT_3) or free thyroxine (FT_4) levels above their upper reference limits. These 390 individuals (242 women) were excluded from further analysis. This resulted in a final study population of 2910 subjects (1469 women) who were available for the present study. The median follow-up time was 5 years (15 284 person-years).

Assessments

Socio-demographic characteristics, smoking status, parental and medical history of hypertension as well as information on the use of antihypertensive drugs were assessed by computer-assisted personal interviews. After a 5 min rest period, heart rate as well as systolic and diastolic blood pressure was measured thrice at the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan), with each reading being followed by a further rest period of 3 min. The mean of the second and third measurements was calculated and used for the present analyses. Systolic and diastolic blood pressures of ≥ 140 and ≥ 90 mmHg respectively were considered as an increase. Pulse pressure was defined as the difference between mean systolic and diastolic pressures. Increased pulse pressure was present if values were above the 75th percentile of the pulse pressure distribution. Hypertension was defined as increased systolic or diastolic blood pressure or use of antihypertensive medication. Height and weight were measured for the calculation of the body mass index (BMI = weight (kg)/height^2 (m^2)). Overweight was defined as BMI values ≥ 25 kg/m^2 and obesity as BMI values ≥ 30 kg/m^2.

Blood samples were taken and laboratory parameters were analyzed in one central laboratory. In the baseline SHIP investigations, serum TSH levels were analyzed by an immunochemiluminescent procedure (LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). The functional sensitivity of the assay was 0.03 mIU/l. The reference range recently established for the SHIP region was 0.25–2.12 mIU/l (14). In the follow-up investigation, serum TSH levels were also analyzed by an immunochemiluminescent method (Immulite 2000, Third Generation, Diagnostic Products Corporation (DPC), Los Angeles, CA, USA). Method comparison of the DPC method against the Byk-Sangtec method yielded a high correlation coefficient ($r = 0.97$) and revealed a regression equation, according to Passing–Bablok, of $y = 1.029^* \times - 0.032$ mU/l (15). All serum TSH levels from the follow-up investigation were corrected using this formula. At baseline, serum FT_3 (LUMItest, Brahms, Berlin, Germany) and FT_4 levels (Byk Sangtec Diagnostica GmbH) were measured by immunochemiluminescent procedures. Serum TSH levels below 0.25 mIU/l with FT_3 and FT_4 within the reference range ($FT_3 \leq 7.0$ pmol/l and $FT_4 \leq 18.9$ pmol/l) (14) were defined as subclinical hyperthyroidism.

Statistical analyses

Categorical data are given as numbers or percentages as indicated; continuous data are given as medians (25th and 75th percentile). The study population was divided into two groups according to the presence or absence of subclinical hyperthyroidism at baseline. Comparisons between groups were made using χ^2 test (nominal data) and Wilcoxon test (continuous data). Comparisons between baseline and follow-up data were made using Wilcoxon signed-rank test. Because the prevalence of hypertension was $>10\%$ in our study sample, odds ratios would overestimate the relative risk (RR).

To estimate the RR from multivariable analysis with dichotomous variables as outcome, we performed Poisson regression with Hubert–White S.E.M. (16). Multivariable analysis of covariance was used to investigate the association between thyroid function and the continuously distributed blood pressure variables for the cohort data. Adjusted RRs or point estimates and their 95% CI were calculated. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

To assess the sensitivity of our results to non-response and dropout, we applied statistical weights. The aim of this approach is to give more weight to subjects whose propensity to drop out of the study is high. The weights accounted for non-response to baseline (SHIP-0) and for dropout to follow-up (SHIP-1) based on socio-demographic and health-related variables. Robust S.E.M. were computed for all weighted analyses.

Results

The median follow-up time was 5 years (15 284 person-years). There were 203 individuals (7.0%, 109 women) with subclinical hyperthyroidism at baseline. These subjects were older, had higher BMI values and a higher proportion of overweight individuals than subjects who had normal serum TSH levels. Both groups were similar with respect to gender, smoking status and obesity (Table 1).

In the whole population, the median systolic blood pressure decreased from 134 mmHg (121; 148 mmHg) at baseline to 131 mmHg (118; 144 mmHg) at follow-up ($P<0.001$). Likewise, diastolic blood pressure decreased from 83 mmHg (76; 90 mmHg) to 80 (74; 88 mmHg, $P<0.001$) and pulse pressure decreased from 50 mmHg (42; 60 mmHg) to 48 (40; 58 mmHg, $P<0.001$). At follow-up, 286 subjects were newly diagnosed as being hypertensive (5-year incidence 19.9%). Testing the bivariate association without considering confounding variables, subjects with subclinical hyperthyroidism more often had hypertension than reference subjects (5-year hypertension incidence 31.4 vs 19.2%; risk ratio 1.64; 95% CI 1.17–2.28, $P=0.006$). Differences between the exposure groups with respect to systolic and diastolic blood pressure or pulse pressure were not statistically significant (Table 2).

Table 1 Baseline characteristics according to subclinical hyperthyroidism.

	Subclinical hyperthyroidism at baseline		
	No ($n=2707$)	Yes ($n=203$)	***P*** [a]
Gender (male)	1347 (49.8%)	94 (46.3%)	0.342
Age (years)	48 (36; 60)	59 (48; 66)	<0.001
Cigarette smoking status			
Never-smoker	1090 (40.3%)	80 (39.4%)	0.217
Ex-smoker	923 (34.1%)	80 (39.4%)	
Current smoker	694 (25.6%)	43 (21.2%)	
Body mass index (kg/m^2)	26.7 (23.7; 29.8)	27.2 (24.9; 29.8)	0.042
Overweight[b]	1748 (64.6%)	150 (73.9%)	0.007
Obesity[c]	661 (24.4%)	46 (22.7%)	0.573

Data are given as numbers (%) or median (25th and 75th percentile).
[a]χ^2 test (nominal data) or Kruskal–Wallis test (interval data).
[b]Overweight was defined as body mass index $\geq$25 kg/m^2.
[c]Obesity was defined as body mass index $\geq$30 kg/m^2.

Table 2 Blood pressure-related variables according to subclinical hyperthyroidism.

	Subclinical hyperthyroidism at baseline		
	No ($n=2707$)	Yes ($n=203$)	***P*** [a]
Hypertension			
No	1090 (40.3%)	59 (29.1%)	0.012
Baseline only	252 (9.3%)	20 (9.9%)	
Follow-up only	259 (9.6%)	27 (13.3%)	
Baseline and follow-up	1106 (40.9%)	97 (47.8%)	
Systolic blood pressure (mmHg; baseline)	133.5 (120.5; 147.5)	136.0 (123.5; 149.5)	0.059
Increased systolic blood pressure $\geq$140 mmHg (baseline)	1019 (37.6%)	88 (43.4%)	0.106
Diastolic blood pressure (mmHg; baseline)	82.5 (75.5; 90.5)	84.0 (77.0; 91.0)	0.446
Increased diastolic blood pressure $\geq$90 mmHg (baseline)	735 (27.2%)	61 (30.1%)	0.372
Pulse pressure (mmHg; baseline)	49.5 (41.5; 59.5)	51.5 (42.5; 62.5)	0.053
Increased pulse pressure $\geq$59.5[b] mmHg (baseline)	732 (27.0%)	67 (33.0%)	0.066

Data are given as numbers (%) or median (25th and 75th percentile).
[a]χ^2 test (nominal data) or Kruskal–Wallis test (interval data).
[b]75th percentile of the pulse pressure distribution.

We further performed multivariable analyses to study the association between subclinical hyperthyroidism and the progression of blood pressure-related variables (Table 3). We found no statistically significant association between subclinical hyperthyroidism and any of the blood pressure-related variables in the whole study population. For sensitivity analyses, we separated all subjects who reported any prevalent or incident thyroid disease or were on antithyroid medication at baseline or follow-up from our study leaving a disease-free population of 2285 subjects (1041 women). There was also no statistically significant association between subclinical hyperthyroidism and blood pressure-related variables in this subpopulation (Table 3).

To test whether possible misclassification in the exposure variable influenced the results of multivariable analyses, we set the TSH cut-off for the definition of subclinical hyperthyroidism to <0.1 mIU/l. There were 44 subjects (1.5%, 32 women) who fulfilled this strict criterion. In Poisson regression analyses, they had a similar risk of hypertension at follow-up (RR 1.67, 95%

Table 3 Association of subclinical hyperthyroidism with progression of blood pressure-related variables and incident hypertension.

	Whole population ($n=2910$)	**Disease-free population** ($n=2285$)
β (95% confidence interval)		
Systolic blood pressure (mmHg)	1.39 (−0.80 to 3.58) $P=0.215$	0.17 (−2.76 to 3.10) $P=0.909$
Diastolic blood pressure (mmHg)	0.94 (−0.32 to 2.19) $P=0.144$	0.42 (−0.99 to 2.39) $P=0.417$
Pulse pressure (mmHg)	0.49 (−1.00 to 1.99) $P=0.518$	−0.46 (−2.43 to 1.52) $P=0.651$
Relative risk (95% confidence interval)[a]		
Increased systolic blood pressure ≥140 mmHg	1.19 (0.85 to 1.68) $P=0.311$ ($n=1803$)	1.09 (0.67 to 1.77) $P=0.742$ ($n=1414$)
Increased diastolic blood pressure ≥90 mmHg	1.05 (0.65 to 1.70) $P=0.850$ ($n=2114$)	1.20 (0.67 to 2.16) $P=0.540$ ($n=1654$)
Increased pulse pressure ≥59 mmHg	0.95 (0.67 to 1.34) $P=0.779$ ($n=2168$)	1.01 (0.66 to 1.55) $P=0.963$ ($n=1704$)
Hypertension	1.23 (0.91 to 1.68) $P=0.182$ ($n=1435$)	1.04 (0.65 to 1.67) $P=0.850$ ($n=1292$)

Analysis of covariance for continuous outcome and Poisson regression for dichotomous outcome, adjusted for age, sex, overweight, obesity, smoking status and time between the examinations. Analyses of covariance were additionally controlled for blood pressures at baseline.
[a]Subjects with prevalent disorder at baseline were excluded from analyses. Numbers of subpopulations are given for each analysis.

CI 0.80–3.49, $P=0.173$) as subjects with serum TSH levels in the reference range. Likewise, analyses of covariance did not reveal a statistically significant association between the exposure variable and any of the outcome variables listed in Table 3.

We further repeated all multivariable analyses outlined in Table 3 after exclusion of subjects who took antihypertensive medication at either baseline or follow-up. In the remaining population of 1854 subjects (976 women), systolic (126 mmHg (116; 138 mmHg) vs 126 mmHg (115; 138 mmHg), $P=0.092$) and diastolic blood pressure (80 mmHg (74; 87 mmHg) vs 80 mmHg (74; 86 mmHg), $P=0.923$) as well as pulse pressure (46 mmHg (39; 54 mmHg) vs 45 mmHg (38; 53 mmHg), $P=0.032$) were comparable between baseline and follow-up. Both analysis of covariance and Poisson regression failed to reveal a statistical significant association between subclinical hyperthyroidism and blood pressure or hypertension in this subpopulation (Table 4).

Furthermore, we performed sensitivity analyses by including the change in the exposure status as well as change of confounder variables in the multivariable models. All these analyses did not reveal a significant association between subclinical hyperthyroidism and blood pressure-related variables (data not shown).

Table 4 Association between subclinical hyperthyroidism and blood pressure-related variables in subjects without antihypertensive treatment.

	Whole population ($n=1854$)	**Disease-free population** ($n=1488$)
β (95% confidence interval)		
Systolic blood pressure (mmHg)	0.89 (−1.65 to 3.42) $P=0.492$	0.62 (−4.07 to 2.52) $P=0.645$
Diastolic blood pressure (mmHg)	0.99 (−0.55 to 2.53) $P=0.207$	0.64 (−1.39 to 2.62) $P=0.547$
Pulse pressure (mmHg)	−0.15 (−1.90 to 1.60) $P=0.866$	−1.39 (−3.66 to 0.88) $P=0.230$
Relative risk (95% confidence interval)[a]		
Increased systolic blood pressure ≥140 mmHg	1.25 (0.83 to 1.91) $P=0.288$ ($n=1450$)	0.82 (0.41 to 1.65) $P=0.578$ ($n=1165$)
Increased diastolic blood pressure ≥90 mmHg	1.20 (0.67 to 2.14) $P=0.535$ ($n=1533$)	1.06 (0.50 to 2.28) $P=0.874$ ($n=1233$)
Increased pulse pressure ≥59 mmHg	1.07 (0.66 to 1.73) $P=0.213$ ($n=1610$)	0.73 (0.36 to 1.48) $P=0.381$ ($n=1289$)
Hypertension	1.28 (0.85 to 1.91) $P=0.237$ ($n=1347$)	0.99 (0.55 to 1.79) $P=0.968$ ($n=1082$)

Analysis of covariance for continuous outcome and Poisson regression for dichotomous outcome, adjusted for age, sex, overweight, obesity, smoking status and time between the examinations. Analyses of covariance were additionally controlled for blood pressures at baseline.
[a]Subjects with prevalent disorder at baseline were excluded from analyses. Numbers of subpopulations are given for each analysis.

Table 5 Baseline characteristics of the study population compared with non-participants.

	Study population ($n=2910$)	**Excluded subjects** ($n=1400$)[a]	***P***[b]
Gender (male)	1441 (49.5%)	676 (48.3%)	0.448
Age (years)	49.0 (37.0; 61.0)	55.0 (35.0; 69.0)	<0.001
Cigarette smoking status			
Never-smoker	1170 (40.2%)	531 (38.5%)	0.047
Ex-smoker	1003 (34.5%)	451 (32.7%)	
Current smoker	737 (25.3%)	399 (28.9%)	
Body mass index (kg/m^2)	26.8 (23.8; 29.9)	27.1 (23.8; 30.5)	0.076
Overweight[c]	1901 (65.3%)	931 (67.0%)	0.285
Obesity[d]	707 (24.3%)	392 (28.2%)	0.006
Subclinical hyperthyroidism	203 (7.0%)	160 (11.4%)	<0.001
Hypertension	1475 (50.7%)	773 (55.6%)	0.003
Systolic blood pressure (mmHg; baseline)	133.8 (121.0; 148.0)	136.5 (121.0; 151.0)	0.003
Increased systolic blood pressure ≥140 mmHg (baseline)	1107 (38.0%)	608 (43.7%)	0.001
Diastolic blood pressure (mmHg; baseline)	83.0 (76.0; 90.5)	82.0 (74.5; 90.0)	0.027
Increased diastolic blood pressure ≥90 mmHg (baseline)	796 (27.4%)	363 (26.1%)	0.385
Pulse pressure (mmHg; baseline)	49.5 (41.5; 59.5)	52.0 (42.5; 65.5)	<0.001
Increased pulse pressure ≥59.5[c] mmHg (baseline)	742 (25.5%)	487 (35.0%)	<0.001

Data are given as numbers (%) or median (25th and 75th percentile).
[a]Numbers in this column partly do not sum up to 1400 due to missing values.
[b]χ^2 test (nominal data) or Kruskal–Wallis test (interval data).
[c]Overweight was defined as body mass index ≥25 kg/m^2.
[d]Obesity was defined as body mass index ≥30 kg/m^2.

To assess possible bias due to missing values and loss to follow-up, we compared the study population with subjects who participated in the baseline SHIP-0 examinations but were excluded from the study population (Table 5). Subjects who did not belong to the study population were older, more often current smokers, obese, subclinical hyperthyroid and hypertensive than subjects included in the study population. Also, most of the blood pressure values were higher in the excluded than in the included subjects (Table 5). Accounting for non-response and loss to follow-up by applying statistical weighing factors, we consistently did not detect statistical significant associations between subclinical hyperthyroidism and blood pressure-related variables with one exception. In the whole population, subjects with subclinical hyperthyroidism had higher diastolic blood pressure values than reference subjects (adjusted mean difference 1.49 mmHg; 95% CI 0.22; 2.75 mmHg; $P<0.05$). In the disease-free population, however, this difference did not attain statistical significance anymore (adjusted mean difference 1.32 mmHg; 95% CI −0.40; 3.40 mmHg; $P=0.131$).

Discussion

In the present study, we investigated the association between subclinical hyperthyroidism and blood pressure-related variables using data from a prospective population-based cohort study. We found negligible associations between subclinical hyperthyroidism and blood pressure or hypertension. To the best of our knowledge, this is the first time that this issue has been analyzed using longitudinal data.

Our data are in good agreement with the results of a cross-sectional population-based Japanese study that included participants who were not treated for thyroid disease (6). In this study (6), the prevalence of hypertension was similar between 77 subjects with subclinical hyperthyroidism and 3130 subjects with serum TSH levels within the reference range. Our results are also in concordance with findings recently reported from our cross-sectional SHIP data (7). Japan and Germany differ from each other with respect to the iodine supply that is iodine-replete in Japan (17) and formerly iodine-deficient in Germany (11, 18). Both countries also differ considerably with respect to the prevalence of hypertension, which is much higher in Japan than in Germany (19). Moreover, within Germany the prevalence of hypertension is highest in the population of West Pomerania (20). The fact that similar results have been obtained from these two distinct populations supports the notion that subclinical hyperthyroidism is not associated with blood pressure-related variables.

However, the present findings are in contrast to the 1981 Busselton study that was conducted in Australia comprising 2033 participants with subclinical hyperthyroidism who did not have prior thyroid disease (5). The original population comprised 3940 participants corresponding to a response proportion of 64%. Unfortunately, blood samples were only available in ~50% of the subjects (21). Thus, it cannot be fully ruled out that selection might partly explain the differences in the results between our investigation and the Busselton study (5). The present cohort study may be regarded as an extension of our recent analyses

from the cross-sectional data (7). Against this background longitudinal data are needed from studies that have cross-sectionally demonstrated an association between subclinical hyperthyroidism and hypertension.

Current guidelines recommend that subclinical hyperthyroidism should be defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and T_3 concentrations are within their reference ranges (9, 22). In our study, we followed this recommendation with the exception that we used serum FT_3 instead of T_3 levels for definition. The lower serum TSH reference value of 0.25 IU/ml established for our study region (14) is lower than values analyzed from other studies (23–25). Different iodine supplies mainly account for this discrepancy (14). For the present study, a relatively low TSH cut-off might be more appropriate than a higher TSH cut-off since the low cut-off increases the specificity of the definition of subclinical hyperthyroidism. To further increase this specificity, we repeated all multivariable analyses by applying a TSH cut-off of 0.1 IU/ml to define subclinical hyperthyroidism. These analyses confirmed the major results, i.e. subclinical hyperthyroidism was not associated with blood pressure or hypertension.

The lowering of the blood pressure cut-offs for the definition of hypertension at the end of the 1990s has led to an increase in antihypertensive treatment for the past 10 years (26). During follow-up, we observed a decrease in median blood pressure in the whole population. This decrease was no longer present for systolic and diastolic blood pressure when all subjects with antihypertensive medication were excluded from the analyses. Only the small difference in pulse pressure of 1 mmHg attained statistical significance due to the large number of participants. These data suggest that at follow-up hypertension has been treated more vigorously and antihypertensive treatment has been initiated at lower blood pressure levels than at baseline.

The likelihood that measuring error by intra-individual variation of blood pressure lowers the precision in the classification of the dependent variable is higher in follow-up studies than in cross-sectional studies. We attempted to tackle this problem by using standardized protocols for blood pressure measurements at baseline and follow-up. We took blood pressure readings thrice after sufficient rest periods and used only the second and the third readings for statistical analyses. Although we detected all expected risk factors for hypertension in our data, we cannot unequivocally exclude that we missed a weak association between subclinical hyperthyroidism and hypertension due to blood pressure variations.

Subjects who were excluded from the study population due to missing values or loss to follow-up were older than the subpopulation studied in the present investigation. Consequently, the former had more common baseline subclinical hyperthyroidism and hypertension than the latter. Furthermore, as in other population-based studies, health problems were a major reason for non-participation in baseline SHIP-0 (3). To account for these imbalances we introduced weighing factors and repeated all multivariable analyses. These analyses revealed a weak, albeit statistically significant association between subclinical hyperthyroidism and diastolic blood pressure. However, this association was in a biologically implausible direction and present neither in the disease-free subpopulation nor for all other blood pressure-related end points including the dichotomized increased diastolic blood pressure variable. Based on these results, we have no strong indication for the presence of a strong response bias in the present analyses.

We conclude that subclinical hyperthyroidism is not associated with changes in blood pressure, pulse pressure or incident hypertension.

Declaration of interest

The funding sources did not contribute to study design in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. There are no conflicts of interest.

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CLINICAL STUDY

Decreased serum TSH levels are not associated with mortality in the adult northeast German population

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Abstract

Objective: Results of cohort studies on the association between decreased serum TSH levels and mortality are conflicting. Some studies demonstrated an increased mortality risk in subjects with decreased serum TSH levels, others did not. Even meta-analyses revealed contradictory results. We undertook the present study to investigate the association between decreased serum TSH levels and mortality in the large population-based Study of Health in Pomerania (SHIP).

Design and methods: Data from 3651 individuals from SHIP without known thyroid disorders or thyroid treatment were analyzed. Serum TSH, free triiodothyronine, and free thyroxine levels were determined by immunochemiluminescent procedures. Decreased TSH was defined as serum TSH levels below 0.25 mIU/l. Cox regression was used to associate decreased TSH levels with mortality.

Results: The median duration of follow-up was 8.5 years (30 126 person years). During follow-up, 299 individuals (6.9%) died corresponding to a death rate of 9.92 deaths per 1000 person years. Survival time was shorter in subjects with decreased serum TSH levels compared to euthyroid individuals. After adjustment for age and sex, however, there was no association between decreased serum TSH levels and all-cause mortality (hazard ratio: 0.95; 95% confidence interval: 0.67; 1.36). Likewise, decreased serum TSH levels were neither associated with cardiovascular nor with cancer mortality.

Conclusions: There is no independent association of decreased serum TSH levels with all-cause, cardiovascular, and cancer mortality in the adult northeast German population. Although our study has some strengths, we cannot finally conclude on therapeutical implications in individuals with subclinical thyroid diseases.

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Introduction

An association between decreased serum thyrotropin (TSH) levels and increased mortality may be explained by several mechanisms. Thus, decreased serum TSH levels have been reported to be associated with surrogate markers of cardiovascular mortality including carotid wall thickness (1), atrial fibrillation (2, 3), high plasma fibrinogen levels (4), and left ventricular hypertrophy (5, 6). However, results of studies on the association between decreased serum TSH levels or subclinical hyperthyroidism (3, 7–18) and mortality are conflicting. With respect to cardiovascular mortality, most studies (3, 11, 12, 18) and all meta-analyses (10, 14, 17) detected no association between decreased serum TSH levels or hyperthyroidism and mortality, while two studies did detect an association (7, 9). Regarding all-cause mortality, one study (7) demonstrated an increased mortality risk in subjects with decreased serum TSH levels, whereas two others did not (12, 16). Focusing on subclinical hyperthyroidism, four studies (3, 9, 15, 18) did not detect an association with all-cause mortality, while one study in geriatric patients (13) did. With respect to overt hyperthyroidism, one study detected a relationship to all-cause mortality (11). Different results have occurred because of nonconsideration of major confounders in some studies (7, 11, 12), differences in definition of hyperthyroidism or follow-up time, and choice of the study population. Furthermore, some previous studies did not distinguish between subclinical and overt hyperthyroidism (7, 9, 12). The controversy on the association between hyperthyroidism and mortality is currently fostered because even meta-analyses revealed contradictory results. While one meta-analysis demonstrated an increased mortality risk in subjects with decreased serum TSH levels (8), three others did not confirm this finding (10, 14, 17).

With respect to cancer mortality, all available studies (19–24) compared participants after radioiodine treatment with a healthy reference group. Among these

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studies, three detected a positive (21, 22, 24), one an inverse (20), and two (19, 23) no association of hyperthyroidism with cancer mortality.

In summary, current evidence for an association of decreased serum TSH levels with increased mortality is weak and nonconsistent (10, 14, 17). Thus, we investigated the association between decreased serum TSH levels and mortality in the large population-based Study of Health in Pomerania (SHIP) distinguishing between subclinical hyperthyroidism and overt hyperthyroidism.

Materials and methods

Study population

SHIP is a population-based cohort study in West Pomerania, a region in the northeast of Germany. Details on the study design have been published previously (1, 25). In brief, the total population of West Pomerania comprised 212 157 inhabitants. As in most parts of Germany, West Pomerania is a region of former iodine deficiency. During the 1990s, improved iodine supplementation has normalized this deficiency level resulting in a median iodine excretion value of 124 μg/l (26). For SHIP, a sample of the population aged 20–79 years was drawn from population registries. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects. SHIP finally included 4310 participants (2193 women) corresponding to a final response of 68.8% (25). Baseline examinations were conducted between 1997 and 2001. All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Of the 4310 subjects who participated in SHIP, 162 subjects (76 women) had missing data in any of the considered variables, 323 subjects (272 women) reported a known thyroid disorder, 70 subjects (51 women) received thyroid treatment, and 104 subjects (68 women) had serum TSH levels above 2.12 mIU/l. These 659 participants (467 women) were excluded from further analysis resulting in a population of 3651 subjects (1726 women) who were available for the present analysis.

Assessments

Socio-demographic characteristics, history of smoking, known thyroid diseases, use of anti-thyroid treatment, history of myocardial infarction, stroke, and diabetes were assessed by computer-assisted personal interviews. Smokers were categorized into three categories (lifetime nonsmokers, former smokers, and current smokers). Former smokers were individuals who had smoked during their lifetime but not in the last 12 months prior to the time of examination. Height and weight were measured for the calculation of the body mass index (BMI) = weight (kg)/height^2 (m^2). After a 5 min rest period, systolic and diastolic blood pressure were measured three times at the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with each reading being followed by a further rest period of 3 min. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined as increased systolic ($\geq$140 mmHg), diastolic blood pressure ($\geq$90 mmHg), or use of anti-hypertensive medication.

Blood samples were taken in supine position between 0700 and 1600 h, and were analyzed in the core laboratory of the University Hospital Greifswald. TSH, free triiodothyronine (FT_3), and free thyroxine (FT_4) levels were measured by immunochemiluminescent procedures (FT_3 LUMItest, Brahms, Berlin, Germany; TSH and FT_4 LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). The functional sensitivity of the TSH assay was 0.03 mIU/l. The reference range recently established for the SHIP region was 0.25–2.12 mIU/l (27). For determination of this reference range, all participants with a known thyroid disease, thyroid medication, goiter, inhomogeneous or hypoechogenic thyroid echo pattern, at least one thyroid nodule, or positive serum anti-thyroperoxidase (TPO) antibodies were excluded. Decreased TSH was defined using the lower reference level as cutoff. Subclinical hyperthyroidism was defined as serum TSH $<$0.25 mIU/l and FT_3 and FT_4 below the respective upper reference limit (FT_3 $\leq$7.0 pmol/l and FT_4 $\leq$18.9 pmol/l) (27). Overt hyperthyroidism was defined as serum TSH levels $<$0.25 mIU/l and FT_3 or FT_4 above the upper respective reference limit (FT_3 $>$7.0 pmol/l or FT_4 $>$18.9 pmol/l). For analysis regarding TSH in the reference range (0.25–2.12 mIU/l), groups were separated by quintiles. Serum cholesterol was measured enzymatically on a Hitachi 717 (Roche). Plasma fibrinogen concentrations were assayed according to Clauss (28) (Electra analyzer, Instrumentation Laboratory, Barcelona, Spain).

Information on vital status was collected at regular intervals from the time of enrolment into the study through August 31, 2007. Subjects were censored at death or loss to follow-up. The number of months between baseline examination and censoring was used as the follow-up length. The median duration of follow-up was 8.5 years (25th, 7.8; 75th, 9.2). During the 30 126 person years of follow-up, 299 participants (217 men) had died. During the 13 913 person years of follow-up, 299 participants (217 men) had died. Death certificates were requested from the local health authority at the place of death, and coded by a certified nosologist according to the International Classification of Diseases, 10th revision (ICD10). Two internists (H W and M D) independently validated the underlying cause of death, and performed a joint reading together with a third internist (H V) in cases of disagreement.

Statistical analysis

Data on quantitative characteristics are expressed as median and interquartile range. Data on qualitative characteristics are expressed as percent values or absolute numbers, as indicated. The study population was divided into two groups according to decreased serum TSH levels at baseline. Comparisons between groups were made using χ^2-test (qualitative data) or Wilcoxon test (quantitative data). To assess the association between decreased serum TSH levels and mortality, we used Cox proportional hazards regression models with survival in years as dependent variable. Three different regression models were applied. The first crude, the second adjusted for age and sex, and the third additionally adjusted for smoking status, BMI, hypertension, myocardial infarction, stroke, cholesterol, diabetes, and fibrinogen. Additionally, interaction terms of decreased TSH with all covariates were added to the full model. All interactions with a value of $P<0.1$ were retained. The model assumption for the Cox proportional hazards regression models was checked by visual inspection of proportional hazard assumption and Schoenfeld residuals. Kaplan–Meier survival curves were used to illustrate the association between serum TSH levels and all-cause mortality, with differences tested by a log rank test. Hazard ratios (HR) were calculated with a 95% confidence interval (CI). A value of $P<0.05$ was considered statistically significant. This manuscript was written in accordance with the STROBE statement, giving guidelines for reporting results from observational studies (29). All statistical analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the baseline characteristics of individuals with and without decreased serum TSH levels. Of the 3651 individuals available for this analysis, 270 had decreased serum TSH levels (7.4%). Compared to euthyroid subjects, individuals with decreased serum TSH levels were elder, and less often current smokers, but more often former smokers. Furthermore, participants with decreased serum TSH levels were more often hypertensive and overweight, reported more often a history of stroke, and had higher fibrinogen levels.

During follow-up, 299 individuals (6.9%) died corresponding to 9.92 deaths per 1000 person years. More individuals with decreased serum TSH levels (15.98 deaths per 1000 person years) deceased than individuals with serum TSH levels within the reference range (9.45 deaths per 1000 person years; relative risk: 1.67; 95% CI: 1.19, 2.33). Also, survival time was shorter in subjects with decreased serum TSH levels compared to euthyroid individuals (log rank test; $P=0.003$). Proportional hazard assumption was met by all models.

Table 1 Baseline characteristics of individuals stratified by serum TSH levels. Data are given as numbers (percent) or median (25 and 75th percentile).

	Serum TSH levels ≥0.25 mIU/l ($n=3381$)	**Serum TSH levels <0.25 mIU/l** ($n=270$)	***P*[a]**
Sex (males)	1807 (52.4%)	155 (57.4%)	0.111
Age (years)	48.0 (35.0; 62.0)	61.0 (48.0; 69.0)	<0.001
Smoking status[b]			
Former smokers	1138 (33.7%)	111 (41.1%)	0.041
Current smokers	947 (28.0%)	64 (23.7%)	
Hypertension	1724 (51.0%)	161 (59.6%)	0.006
Stroke	67 (2.0%)	15 (5.6%)	<0.001
Myocardial infarction	109 (3.2%)	12 (4.4%)	0.281
Diabetes mellitus type 2	249 (7.4%)	26 (9.6%)	0.175
Body mass index (kg/m^2)	26.7 (23.6; 29.9)	27.4 (24.9; 30.0)	0.029
Cholesterol (mmol/l)	5.7 (4.9; 6.5)	5.6 (4.9; 6.3)	0.231
Fibrinogen (mmol/l)	8.3 (7.3; 9.9)	9.3 (7.9; 10.9)	<0.001
Time of blood collection (before 1200 h)	2038 (60.3%)	168 (62.2%)	0.530

Table refers to subjects without increased serum TSH levels >2.12 mIU/l.
[a]χ^2-test (qualitative data) and Wilcoxon test (quantitative data).
[b]Reference lifetime nonsmokers.

Table 2 displays the association between decreased serum TSH levels and all-cause mortality. The crude model revealed a significant association between decreased serum TSH levels and all-cause mortality. This association was no longer present after adjustment for age and sex. Figure 1 shows the cumulative hazard functions for all-cause mortality by serum TSH levels adjusted for age and sex. Further adjustments for smoking habits, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, BMI, cholesterol, and fibrinogen had only small effects on the results (Table 2). There were also no statistically significant independent associations between decreased serum TSH levels and all-cause mortality when increasing the TSH cutoff to 0.3 mIU/l (7, 9) or 0.4 mIU/l (15, 18) (Table 2). Furthermore, no association between TSH in the reference range (the group below the first quintile was defined as reference group) and mortality was detected (Table 2). Interactions of decreased serum TSH levels with hypertension, myocardial infarction, stroke, serum cholesterol levels, and BMI were sequentially added to model 3. None of these interactions attained statistical significance. Sex-stratified analyses showed no significant association between decreased serum TSH levels and mortality (men: HR, 1.00; 95% CI, 0.66, 1.51; $P=0.997$; women: HR, 0.72; 95% CI, 0.34, 1.51; $P=0.384$) in the full-adjusted models. Also, analyses stratified by the time of blood collection (before and after 1200 h) revealed no change of results.

Table 2 Association of decreased serum TSH levels and TSH levels in the reference range with all-cause mortality.

Exposition[a]	Number of deaths in the exposure group	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
TSH<0.25 mIU/l (n=270)	35	1.69 (1.19; 2.40)†	0.95 (0.67; 1.36)	0.93 (0.65; 1.33)
TSH<0.3 mIU/l (n=396)	49	1.63 (1.20; 2.21)†	0.92 (0.67; 1.25)	0.93 (0.68; 1.27)
TSH<0.4 mIU/l (n=727)	81	1.50 (1.17; 1.94)†	0.91 (0.71; 1.18)	0.93 (0.72; 1.20)
TSH≤0.03 mIU/l (n=15)	2	0.94 (0.23; 3.79)	0.97 (0.24; 3.90)	1.06 (0.26; 4.30)
0.03 mIU/l<TSH<0.25 mIU/l (n=255)	33	1.76 (1.23; 2.51)†	0.96 (0.67; 1.38)	0.93 (0.65; 1.34)
TSH in the reference range				
0.45 mIU/l<TSH≤0.61 mIU/l (n=673)	52	0.72 (0.51; 1.03)	0.93 (0.65; 1.32)	0.91 (0.64; 1.30)
0.61 mIU/l<TSH≤0.78 mIU/l (n=662)	49	0.69 (0.48; 0.99)*	0.99 (0.69; 1.42)	0.93 (0.65; 1.33)
0.78 mIU/l<TSH≤1.05 mIU/l (n=681)	44	0.60 (0.42; 0.88)†	1.06 (0.73; 1.54)	1.09 (0.75; 1.58)
1.05 mIU/l<TSH (n=666)	45	0.64 (0.44; 0.93)*	1.26 (0.87; 1.82)	1.21 (0.83; 1.76)

*P<0.05, †P<0.01. HR, hazard ratio; CI, 95% confidence interval; model 1, unadjusted Cox regression; model 2, Cox regression adjusted for age and sex; model 3, Cox regression adjusted for age, sex, smoking status, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, body mass index, cholesterol, and fibrinogen.
[a]Reference group: euthyroid individuals above the respective cutoff; for analysis regarding the TSH reference range (0.25 mIU/l; 2.12 mIU/l), individuals <0.45 mIU/l (first quintile of TSH in the reference range) are in the reference group.

Of the 299 deceased individuals, the cause of death was not available from 41 individuals. Of the remaining 258 decedents, 96 individuals (25 women; 32.1%) died from cancer (ICD code: C00–C97) and 97 individuals (29 women; 32.4%) from cardiovascular diseases (ICD code: I10–I97). After adjustment for confounders, Cox regression revealed no significant associations of decreased serum TSH levels with cancer (HR, 1.05; 95% CI, 0.57, 1.93; P=0.890) and cardiovascular mortality (HR, 1.08; 95% CI, 0.61, 1.91; P=0.803). When alternating the TSH cutoff to 0.3 mIU/l, Cox regression models disclosed a HR of 1.05 (95% CI, 0.67, 1.63; P=0.846) for cancer and 0.82 (95% CI, 0.52, 1.30; P=0.394) for cardiovascular mortality.

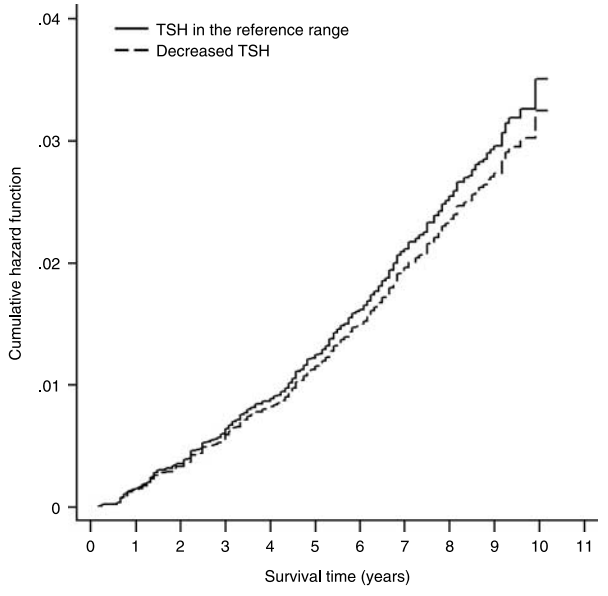

Figure 1 Cumulative hazard functions for participants with and without decreased TSH.

Finally, we divided subjects with serum TSH levels below 0.25 mIU/l into those with subclinical (243 subjects; 103 women) and those with overt hyperthyroidism (27 subjects; 15 women). When applying Cox regression models, there was no association of subclinical or overt hyperthyroidism with all-cause, cancer, and cardiovascular mortality (Table 3).

Discussion

In the present study, we analyzed associations of decreased serum TSH levels with all-cause, cancer, and cardiovascular mortality. We detected no such associations. Applying an alternative cutoff for decreased serum TSH levels as well as dividing individuals with decreased serum TSH levels into those with subclinical and overt hyperthyroidism did not change these results materially.

With respect to decreased serum TSH levels, our results are in line with two studies (12, 16). Two other studies (7, 11) reported an association between decreased serum TSH levels and all-cause mortality. Contrary to one study (11), we detected no relationship between overt hyperthyroidism and all-cause mortality. Focussing on subclinical hyperthyroidism, our results are in concordance with most of the previous studies (3, 9, 15, 18) and meta-analyses (10, 14). However, one study (13) and one meta-analysis (8) did not confirm this finding. Haentjens *et al.* (8) concluded that the increased likelihood of death is not immediate after the diagnosis of subclinical hyperthyroidism, but became apparent after the second year and continued up to 10 years after the diagnosis of subclinical hyperthyroidism. Haentjens *et al.* (8) included seven studies (3, 7, 9, 12, 13, 18, 30) in their meta-analysis. Two of those (7, 12) did not explicitly focus on the association of subclinical hyperthyroidism with all-cause mortality, e.g. Parle *et al.* (12) compared participants with serum TSH levels

Table 3 Association of subclinical and overt hyperthyroidism with all-cause, cancer, and cardiovascular mortality.

	Model 1		Model 2		Model 3	
	Subclinical hyperthyroidism (*n*=243; 31 deaths)	Overt hyperthyroidism (*n*=27; 4 deaths)	Subclinical hyperthyroidism (*n*=243; 31 deaths)	Overt hyperthyroidism (*n*=27; 4 deaths)	Subclinical hyperthyroidism (*n*=243; 31 deaths)	Overt hyperthyroidism (*n*=27; 4 deaths)
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality	1.66 (1.14; 2.41)*	1.98 (0.74; 5.31)	0.94 (0.65; 1.37)	1.01 (0.38; 2.70)	0.91 (0.63; 1.33)	1.08 (0.40; 2.96)
Cancer mortality	1.91 (1.02; 3.57)*	1.61 (0.22; 11.57)	1.07 (0.57; 2.00)	0.81 (0.11; 5.85)	1.05 (0.56; 1.99)	1.07 (0.15; 7.82)
Cardiovascular mortality	1.92 (1.03; 3.61)*	4.57 (1.44; 14.44)*	0.95 (0.50; 1.78)	2.02 (0.64; 6.40)	0.97 (0.51; 1.83)	2.07 (0.63; 6.87)

*$P<0.05$. HR, hazard ratio; CI, confidence interval; model 1, unadjusted Cox regression; model 2, Cox regression adjusted for age and sex; model 3, Cox regression adjusted for age, sex, smoking status, hypertension, stroke, myocardial infarction, diabetes mellitus type 2, body mass index, cholesterol, and fibrinogen.

of ≤ 0.5 mIU/l with those >0.5 mIU/l. Contrary to the meta-analysis by Ochs *et al.* (10), Haentjens *et al.* (8) considered the study by Parle *et al.* (12) as one which has detected a significant association between subclinical hyperthyroidism and mortality. The reason for this is that Parle *et al.* (12) reported estimators for five different follow-up times. For a follow-up time of 10 years, they detected no association but for follow-up times of 2, 3, 4, and 5 years. This might be one explanation for conflicting results between these meta-analyses (8, 10). Also, the selection of studies included might be responsible for conflicting results between these meta-analyses. Völzke *et al.* (17) included two studies into their meta-analyses, Singh *et al.* (14) included three studies, and Ochs *et al.* (10) included five studies. Furthermore, the meta-analysis by Haentjens *et al.* was the first which included studies of patients with co-morbidities (9, 13, 30).

Furthermore, four (7, 12, 13, 30) of the seven studies included in the meta-analysis by Haentjens did not adjust their models for major confounders such as age and smoking. Particularly, smoking is an important risk factor in the pathogenesis of thyroid diseases (31, 32). Because smoking is also an important predictor of mortality (33), the impact of hyperthyroidism on mortality might be overestimated when smoking is not considered (17). In our analysis, a statistically significant association between decreased serum TSH levels and mortality was no longer present even after adjustment for age. Since different studies did not adjust for the same covariables, it should be decided carefully which studies to include into a meta-analysis. Conclusions from meta-analyses may be hampered, if they include original results from multivariable analyses adjusted for different sets of covariables. In our study, confounders apart from age and sex did not change the results materially, but in other populations, these confounders might play a more important role.

Apart from different nonconsideration of major confounders, there are three further factors that might be responsible for contradictory results. Firstly, different definitions of hyperthyroidism might have led to conflicting results. Usually, the cutoff for serum TSH levels varied between 0.3 (7) and 0.5 mIU/l (12). Most of these studies considered FT_4 levels (3, 9, 11, 13, 15, 16, 18), whether others did not (7, 12). Secondly, differences in follow-up time play a crucial role. In previous studies on the association between hyperthyroidism and mortality, the mean follow-up time varied between 3.7 (7) and 20 years (18). Short follow-up times in smaller studies might be problematic, since the impact of the disease on mortality might be too weak. Otherwise, analysis based on long follow-up times might underestimate the influence of the exposure on mortality for misclassification bias due to change in exposure over time. In the present study, participants were informed about their laboratory results. The awareness of thyroid diseases might have led to frequent medical monitoring and early treatment decisions, which also might have introduced bias due to change in the exposure variable. This might have resulted in an underestimation of the effect of hyperthyroidism on mortality in the present study, particularly for overt hyperthyroidism. Finally, different age structures of the selected populations might have given rise to discrepant results. Some of previous studies on the association of hyperthyroidism with mortality focused on participants older than 60 years (3, 7, 12, 13, 15).

With respect to cardiovascular mortality, results from our study are in concordance with most of the previously reported studies (3, 11, 12, 18) and meta-analyses (10, 14, 17). Two other studies (7, 9) detected an association between decreased serum TSH levels and cardiovascular mortality. Although Iervasi *et al.* (9) detected no association between mild hyperthyroidism with all-cause mortality, they demonstrated that mild hyperthyroidism is an independent risk factor for cardiovascular mortality in their study. Results from this study (9) are not comparable to those from our study because they investigated this association in a subgroup of cardiac patients. While the association between decreased serum TSH levels and cardiovascular mortality is conflicting, the association between decreased serum TSH levels and nonfatal events

including atrial fibrillation (3), high plasma fibrinogen levels (4), and left ventricular hypertrophy (6) is well established. Parts of this discrepancy might be explained by the fact that atrial fibrillation *per se* is at least not tightly related to increased mortality (34). Furthermore, one might assume that patients having subclinical hyperthyroidism diagnosed at the time of a cardiovascular event might be treated for the thyroid disorder or referred to a more intense clinical follow-up.

In concordance with two studies (19, 23), we detected no association between hyperthyroidism and cancer mortality, while three studies (20–22, 24) demonstrated such an association. However, these studies did not use population-based samples (19–24), but were conducted in patient cohorts undergoing radioiodine treatment. It is the objective of current research to answer the question whether increased mortality in these patients might be related to the exposure of ionizing radiation. Selection bias might represent an alternative explanation for the increased mortality in radioiodine patients. At least in some regions only, those patients undergo radioiodine treatments that have contraindications against surgery, i.e. elder patients with co-morbidities. Thus, increased mortality in these patients might be related to age and poor general condition rather than to thyroid dysfunction or radioiodine application.

The size of the study population represents a major limitation of the present study. Although in the present study risk estimators were mostly close to 1, a weak association between decreased serum TSH levels and all-cause mortality with an HR of <1.65 might have been missed from detection due to power reasons. In particular, the number of subjects who were classified as overt hyperthyroid and those who died from cancer and cardiovascular diseases was too low. Therefore, further research is strongly needed in that respect. Another limitation of our study is the less well-standardized time of blood specimen collection. It has been previously reported that serum TSH levels might alter by daytime (35). Therefore, we performed analyses stratified by the time of blood sampling, which did not change the results materially. Strengths of our study include the population-based approach and the definition of thyroid dysfunction using not only TSH but also free thyroid hormones.

In conclusion, we detected no independent association of decreased serum TSH levels with all-cause, cancer, and cardiovascular mortality in the adult northeast population of Germany. Although our study has some strengths, we cannot finally conclude on therapeutical implication to treat or not to treat individuals with subclinical thyroid diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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