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Abkürzungsverzeichnis

Abkürzung	Erklärung
ADHS	Aufmerksamkeitsdefizit-Hyperaktivitätsstörung
BMI	Körpermassenindex (engl.: body mass index)
CV	Interseriellen Variationskoeffizienten (engl.: coefficient of variation)
fT3	Ungebundenes (freies) Trijodthyronin (engl.: free triiodothyronine)
fT4	Ungebundenes (freies) Thyroxin (engl.: free thyroxine)
HPT-Achse	Hypothalamus-Hypophysen-Schilddrüsen Achse (engl.: Hypothalamus-Pituitary-Thyroid Axis)
ICD-10	10. Version der internationalen statistischen Klassifikation der Krankheiten und verwandter Gesundheitsprobleme (engl.: International Statistical Classification of Diseases and Related Health Problems, 10th edition)
IgG	Immunglobulin G
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
mU/L	Internationale Millieinheiten pro Liter
PSU	Primäre Stichprobeneinheiten (engl.: primary sample units)
SDQ	Fragebogen zu Stärken und Schwächen (engl.: Strengths and Difficulties Questionnaire)
SES	Sozioökonomischer Status (engl.: socio-econcomic status)
SOP	Standardvorgehensweise (engl.: standard operating procedure)
TSH	Thyrotropin (engl.: thyroid stimulating hormone)
ZUMA	Zentrum für Umfrageforschung und Methodik

Einleitung

Definition, Ursachen und Epidemiologie der Aufmerksamkeitsdefizit-Hyperaktivitätsstörung

Die Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHS) ist eine der häufigsten psychischen Erkrankungen bei Kindern und Jugendlichen und zeigt eine ansteigende Prävalenz.[1] Die Symptome sind durch Konzentrations- und Aufmerksamkeitsschwierigkeiten, einer beeinträchtigten Verhaltenskontrolle und durch Hyperaktivität gekennzeichnet.[2] ADHS betrifft aktuell weltweit etwa 7,1% aller Kinder und Jugendlichen[3] und übersteigt damit frühere Schätzungen von 5,3%.[4] Bei 65% aller Fälle dauern die Symptome bis ins Erwachsenenalter an.[5]

ADHS zeigt eine signifikante klinische Heterogenität in Bezug auf die Symptomschwere, die Kombination unterschiedlicher Symptome, den Entwicklungsverlauf und die vorhandenen Komorbiditäten. Diese Parameter werden durch vererbte und nicht vererbte Faktoren beeinflusst. Genetische Varianten (d.h. Einzelnukleotid-Polymorphismen) sind wahrscheinlich an der Pathophysiologie von ADHS beteiligt.[6] Ihre Effektgrößen sind jedoch eher gering. Interessanterweise wurde in Zwillings- und Adoptionsstudien[7] eine hohe durchschnittliche Heritabilität von 0,77 gefunden. Auch endokrine Störungen beeinflussen die Anfälligkeit für ADHS. Umweltgifte, wie z.B. die Belastung durch Blei, Organophosphat-Pestizide und polychlorierten Biphenyle, denen Kinder pränatal oder während der frühen Kindheit ausgesetzt sind, sind Risikofaktoren für ADHS.[8] Endokrin wirksame Chemikalien, wie Monoethylhexyl Phthalate sind ebenfalls mit einem erhöhten Risiko für ADHS assoziiert.[9] Die Prädisposition für ADHS wird jedoch entsprechend der aktuellen Literatur und dem Forschungsstand nicht durch Fehlernährung (z.B. Zucker und künstliche Lebensmittelfarbstoffe) und Nahrungsmittel mit niedrigem oder hohem Immunglobulin G (IgG) beeinflusst.[10] Weitere Erkenntnisse deuten darauf hin, dass es keinen kausalen Zusammenhang zwischen mütterlichem Rauchen während der Schwangerschaft und ADHS beim Nachwuchs gibt.[11] Eine kürzlich veröffentlichte Meta-Analyse lieferte zwar Hinweise auf einen Zusammenhang zwischen mütterlichem Rauchen und ADHS bei den Nachkommen[12], die Autoren berichteten jedoch auch eine signifikante Heterogenität zwischen den Studien (I^2 = 79,2%, p< .01).

Mütterliche Schilddrüsenfunktion während der Schwangerschaft

Eine mütterliche Schilddrüsenfehlfunktion kann die fetale Gehirnentwicklung negativ beeinflussen. Ärztliche diagnostizierte mütterliche Hyperthyreose,[13, 14] hohe Thyrotropin (TSH) Werte während der Schwangerschaft[15] und mütterliche Autoimmunthyreoiditis[16] in der Frühschwangerschaft erhöhen das Risiko des Nachwuchses für ADHS. Die verheerenden Folgen eines schweren Jodmangels während der Schwangerschaft für die neurologische Entwicklung von Föten und Kindern sind allgemein bekannt.[17] Darüber hinaus werden auch die möglichen Auswirkungen eines weniger schweren Jodmangels während der Schwangerschaft auf die kognitive Entwicklung der Nachkommen zunehmend erkannt.[18] Obwohl es einen Zusammenhang zwischen mütterlicher Schilddrüsenfehlfunktion und ADHS bei den Nachkommen gibt,[19] existiert wenig Literatur zu Jodsupplementation in der Schwangerschaft und dem Risiko für ADHS bei den Nachkommen.

In einer großen norwegischen Kohortenstudie wurde kein signifikanter Zusammenhang zwischen der mütterlichen Jodzufuhr und der ADHS-Diagnose bei Kindern gefunden, wohl aber mit den ADHS-Symptomen.[20] Dies wird durch eine große dänische Kohortenstudie bestätigt[14]. Die Jodzufuhr ist der Schlüsselfaktor für eine gute Funktion der Schilddrüse. Eine Jodunterversorgung, die kausal zu einer Schilddrüsendysfunktion führt und damit das Risiko eines ADHS möglicherweise erhöht, ist vor allem bei Schwangeren in sonst ausreichend versorgten Regionen in Europa[21], aber auch in der Allgemeinbevölkerung weltweit nachzuweisen.[22]

Schilddrüsenfunktion bei Kindern und Jugendlichen

Da die Synthese und Sekretion von Schilddrüsenhormonen durch ein negatives Rückkopplungssystem reguliert wird, an dem der Hypothalamus, die Hypophyse und die Schilddrüse beteiligt sind (die HPT-Achse),[24] ist die Schilddrüsenfunktion wichtig für die kognitive Entwicklung von Kindern und Jugendlichen.[23] Da Personen mit Hyperthyreose ADHS-ähnliche Symptome aufweisen können (z. B. Ängstlichkeit, Nervosität, Reizbarkeit und körperliche Hyperaktivität),[25] untersuchten mehrere Studien den Zusammenhang zwischen Schilddrüsendysfunktion und ADHS bei Kindern. Zader et al. schlussfolgerten, dass Kinder mit Hyperthyreose ein ADHS-Prävalenzverhältnis von 1,7 im Vergleich zu Kindern ohne Hyperthyreose aufweisen. Darüber hinaus ging in 40% der Fälle die psychische Diagnose der Hyperthyreose um 90 Tage voraus, wobei in 68,3% der Fälle ADHS vor der Hyperthyreose diagnostiziert wurde.[26] Selbst innerhalb des Referenzbereichs waren TSH-

Konzentrationen im oberen Quartil positiv mit ADHS-Symptomen bei gesunden Kindern assoziiert.[27] Bei Jugendlichen wurde eine Schilddrüsenfehlfunktion jedoch nicht mit ADHS in Verbindung gebracht.[28] Frühe Studien mit klinisch diagnostizierten ADHS-Kindern und Jugendlichen waren hinsichtlich der Schilddrüsenfehlfunktion nicht eindeutig. Einige Studien unterstützten einen Zusammenhang zwischen Anomalien der Schilddrüsenfunktion und den kognitiv-verhaltensbezogenen Manifestationen von ADHS,[29] während andere dies nicht aufweisen konnten.[30] So zeigten frühere Studien eine große Heterogenität, was teilweise auf die relativ kleinen Stichprobengrößen von 150 [28, 30] bis 350 [27, 29] ausgewerteten ADHS-Fällen zurückzuführen sein könnte.

Ziele der Studie

Wir assoziierten TSH sowie die zirkulierende Schilddrüsenhormone freies Trijodthyronin (fT3) und freies Thyroxin (fT4) mit dem ADHS-Risiko unter Verwendung von Querschnittsdaten aus der bevölkerungsbasierten Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS). Spezifisch untersuchten wir zunächst, ob und in welchem Ausmaß die Serumkonzentration von TSH, fT3 und fT4 mit ADHS-Symptomen und der ADHS-Diagnose assoziiert sind. Unsere Regressionsmodelle wurden für eine Vielzahl möglicher Confounder adjustiert, die nach Literaturrecherche sowohl mit der Schilddrüsenfunktion als auch mit der ADHS assoziiert waren. Berücksichtigt wurde u.a. das Geschlecht, da Jungen im Vergleich Mädchen dreimal häufiger an ADHS erkranken. Im Erwachsenenalter ist die Wahrscheinlichkeit, an ADHS zu erkranken, bei Männern und Frauen gleich hoch.[31] In Übereinstimmung mit diesem Befund deuten neuere Forschungsergebnisse darauf hin, dass Veränderungen im Symptomprofil von ADHS, bei denen Hyperaktivität in der Kindheit bei Männern, später in der Adoleszenz jedoch bei Frauen auftritt, zu diesem Muster beitragen könnten.[32] In das Modell wurde ebenfalls der Body-Mass-Index (BMI) mit aufgenommen, da frühere Meta-Analysen eine signifikante Assoziation zwischen Übergewicht bzw. in extremen Fällen Fettleibigkeit und ADHS zeigten.[33, 34] Darüber hinaus wurde in mehreren Kohorten- und Metaanalysen ein signifikanter Zusammenhang zwischen niedrigem Geburtsgewicht bzw. Frühgeburtlichkeit und ADHS gefunden.[35, 36] Da mütterliches Rauchen ein Risikofaktor für niedriges Geburtsgewicht und Frühgeburtlichkeit ist,[37, 38] wurde dieser Störfaktor, neben dem Geburtsgewicht, ebenfalls in die Regressionsanalyse aufgenommen. Zusammenfassend haben wir das Geschlecht und das Geburtsgewicht, das Alter und den BMI der Kinder, sowie das mütterliche Rauchverhalten während der Schwangerschaft als Kovariaten in die Regressionsanalyse einbezogen.

Methoden

Teilnehmende und Studiendesign

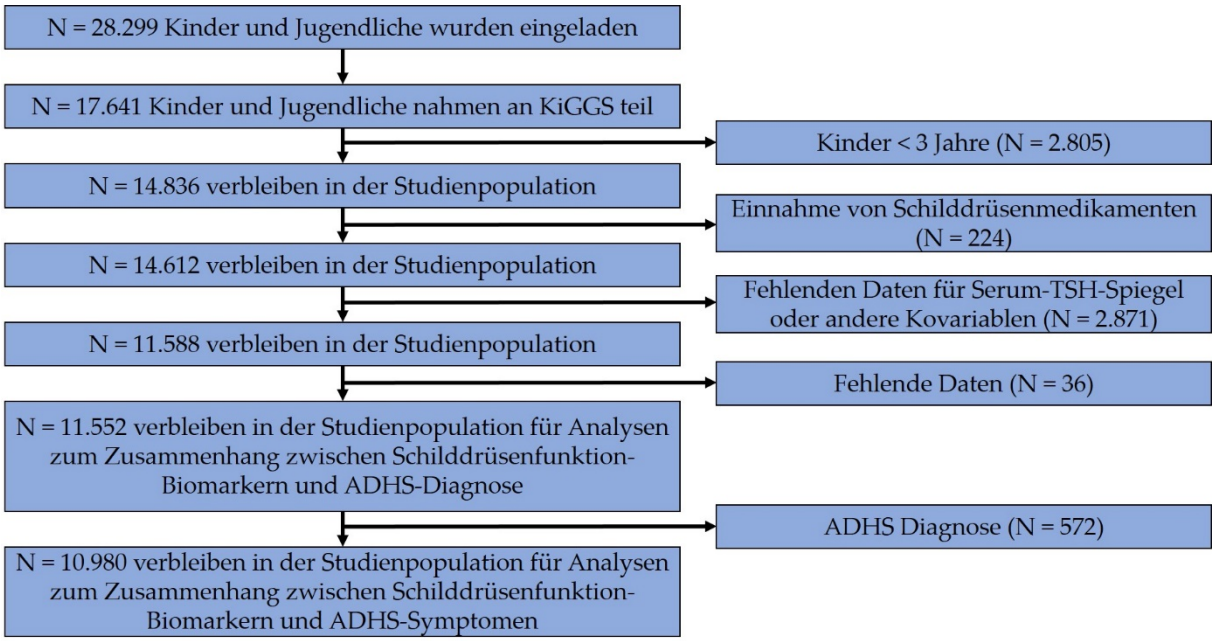
Die Basisdaten Erhebung der bevölkerungsbasierten Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) basiert auf einer national repräsentativen Querschnittsstichprobe von Kindern und Jugendlichen im Alter von 0-17 Jahren mit Hauptwohnsitz in Deutschland.[39] Das Stichprobenverfahren folgte einem zweistufigen Protokoll, das in Zusammenarbeit mit dem Zentrum für Umfrageforschung und Methodik (ZUMA) aus Mannheim, Deutschland, entwickelt wurde. Um die Bevölkerungsgröße nach Urbanisierungsgrad und geografischer Verteilung in Deutschland proportional zu berücksichtigen wurden zunächst 167 Gemeinden als primäre Stichprobeneinheiten (PSUs) ausgewählt. Um eine ausreichende Stichprobengröße für die Analysen zu gewährleisten, wurden Studienpopulation nach Wohnsitz in Ost- oder Westdeutschland stratifiziert. Dabei wurde eine überproportionale Anzahl an PSUs gezogen, um das ehemalige West- (n= 112) und Ostdeutschland (n = 50), sowie Berlin (n = 5) abzubilden[40]. In der zweiten Stufe wurde acht Wochen vor Untersuchungsbeginn eine gleiche Anzahl von Adressen (n=24) pro Geburtskohorte zufällig aus lokalen Einwohnermelderegistern innerhalb der selektierten PSUs ausgewählt (einfache Zufallsstichprobe). Eine letzte einfache Zufallsstichprobe wurde am Robert-Koch-Institut (Berlin, Deutschland) gezogen, die je nach Gemeindegröße insgesamt acht, neun oder zehn Kinder und Jugendliche pro Geburtskohorte umfasste. Die gesamte KiGGS-Baseline-Stichprobe umfasste 28.299 Kinder und Jugendliche. Die Ethikkommission der Charité/Universitätsmedizin Berlin genehmigte die Studie.

Die Eltern der teilnahmeberechtigten Kinder und Jugendlichen wurden per Brief angeschrieben und zur Teilnahme an der Studie eingeladen. Nach einem zufälligen Routenplan wurden innerhalb von drei Jahren (19.05.2003 bis 06.05.2006) 167 PSUs von vier Studienteams bereist und die Untersuchungen durchgeführt. Zu denjenigen, die auf das Einladungsschreiben nicht antworteten, wurde der persönliche Kontakt gesucht. Insgesamt nahmen 17.641 Kinder und Jugendliche an der Studie teil (Rücklauf 66,6%). Die Eltern aller Teilnehmenden haben eine schriftliche Einverständniserklärung gegeben.

Von unserer Analyse der 17.641 KiGGS-Baseline-Teilnehmenden wurden Kinder, die jünger als drei Jahre waren, ausgeschlossen (n=2.805), da die Blutprobenmenge für die Messung der Schilddrüsenhormone nicht ausreichend war. Weiterhin schlossen wir 224 Teilnehmende aus, die Schilddrüsenmedikamente einnahmen, und 2.871 Teilnehmende mit fehlenden Daten für

Serum-TSH-Spiegel oder Kovariablen, so dass 11.588 Teilnehmende in die Analyse von Schilddrüsenfunktions-Biomarkern und ADHS-Diagnose eingeschlossen wurden. Für die zweite Regressionsanalyse, die den Zusammenhang zwischen Schilddrüsenfunktion-Biomarkern und ADHS-Symptomen untersuchte, fehlten bei 36 Teilnehmenden Daten für die Confounder. Außerdem wurden hier die 572 Personen mit einer ADHS-Diagnose ausgeschlossen, was zu einer endgültigen Stichprobengröße von 10.980 Kindern und Jugendlichen führte. Die Zusammensetzung der Studienpopulation ist schematisch in Abbildung 1 abgebildet.

Abbildung 1 – Schematische Darstellung der Zusammensetzung der Studienpopulation.



TSH – Thyrotropin (engl.: thyroid stimulating hormone, - TSH), ADHS = Aufmerksamkeitsdefizit-Hyperaktivitätsstörung, KiGGS - Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland.

Interview und körperliche Untersuchung

Das auf die Altersgruppe angepasste Untersuchungs- und Interviewprogramm wurde in einer Standard Operating Procedure (SOP)-konformen, standardisierten Weise durchgeführt. Jedes an der Studie beteiligte Team, das aus einem Arzt bzw. einer Ärztin und zwei Untersucher:innen bestand, nahm vor Beginn der Feldarbeit an einem umfassenden Schulungsprogramm teil, in dem die in den SOP-Handbüchern festgelegten Richtlinien erläutert wurden. Während der Datenerhebungsphase wurden bei Bedarf regelmäßig Nachschulungen durchgeführt. Alter, Geschlecht, Geburtsgewicht, Schwangerschaftswoche bei der Geburt sowie mütterliches Rauchen während der Schwangerschaft (regelmäßig, gelegentlich, nie) und der sozioökonomische Status (SES) der Familie, der auf Basis eines

etablierten und validierten Index von Winkler und Stolzenberg[41] als "niedrig", "mittel" oder "hoch" definiert wurde, wurden mittels computergestützter Elterninterviews durch einen Studienarzt ermittelt. Der multidimensional aggregierte SES-Index umfasst die Dimensionen Bildung der Eltern (Schulbildung und berufliche Qualifikation), Einkommen (Haushaltsnettoeinkommen aller Haushaltsmitglieder) und beruflicher Status. Zusätzlich wurde ein breites Spektrum an Gesundheitsinformationen durch einen selbst auszufüllenden Fragebogen erhoben. Diese Fragebögen waren kinderaltersgruppenspezifisch und wurden den Eltern aller Teilnehmenden im Alter von 0 bis 17 Jahren und zusätzlich direkt den Teilnehmenden im Alter von 11 bis 17 Jahren vorgelegt. Der Elternfragebogen beinhaltete die Frage, ob bei ihrem Kind eine ADHS-Diagnose nach dem etablierten Symptomprofil (10. Auflage; ICD-10[42]) durch ein Multi-Informanten-Assessment gestellt wurde.[2] Aus dem bereits häufig getesteten und validierten Strengths and Difficulties Questionnaire (SDQ)[43] wurde die Subskala Unaufmerksamkeit /Hyperaktivität in den Elternfragebogen aufgenommen. Zur Bestimmung der ADHS-Symptomatik wurde der Cut-off-Wert der englischen Referenzstichprobe verwendet,[44] der mit dem deutschen Cut-off-Wert identisch ist.[45] Die interne Konsistenz der Subskala Unaufmerksamkeit/Hyperaktivität beträgt $\alpha = 0{,}59$ und variiert von 0,52 (niedrigster Wert, Altersgruppe 3-6 Jahre) bis 0,63 (höchster Wert, Altersgruppe 11-13 Jahre).[46] Obwohl im KiGGS-Studiensetting eine Mehrpersonenbeurteilung nicht durchführbar war, wurde unabhängig von der elterlichen Unaufmerksamkeit/Hyperaktivitätsbeurteilung eine zusätzliche Verhaltensbeurteilung durch das Studienteam während der körperlichen Untersuchung (n= 7.919) für die Altersgruppe der 3- bis 11-Jährigen durchgeführt. Die Kriterien für die vom Studienteam durchgeführte Verhaltensbeurteilung orientierten sich an den drei Hauptsymptomen der ADHS: Unaufmerksamkeit, Unruhe und Impulsivität. Anhand der Elternfragebögen wurden die Teilnehmende als ADHS-Diagnosefälle kategorisiert, wenn ein Arzt oder Psychologe zuvor ADHS diagnostiziert hatte. Die ADHS-Symptomatik wurde wie folgt bestimmt: Teilnehmende im Alter von 3 bis 11 Jahren, die einen Summenwert von ≥ 7 in der Skala Unaufmerksamkeit/Hyperaktivität des SDQ erzielten und zusätzlich eine positive Verhaltensbeurteilung durch das Studienteam erhielten, jedoch keine vorherige ADHS-Diagnose hatten, wurden dieser Gruppe zugeordnet. Bei Teilnehmenden, die älter als 11 Jahre waren, bestimmte das Ergebnis der SDQ-Subskala die ADHS-Symptomatik. Die Teilnehmenden wurden in unserer ersten Analyserunde der Kontrollgruppe zugeordnet, wenn keine vorherige ADHS-Diagnose attestiert wurde. In unserer zweiten Analyserunde bestand die Kontrollgruppe aus Teilnehmenden ohne vorherige ADHS-Diagnose, deren

Verhaltensbeurteilung und das Ergebnis der SDQ-Subskala auf keine ADHS-Symptome hinwiesen.

Der BMI der Teilnehmenden wurde berechnet, indem das Körpergewicht in kg durch die Körpergröße in cm zum Quadrat geteilt wurde, die bei der körperlichen Untersuchung gemessen wurde. Die Tanner-Skala wurde vom Untersucher erfasst und zur Beschreibung der körperlichen Entwicklung verwendet.[47] Die Tanner-Stadien eins bis fünf wurden anhand der äußeren primären und sekundären Geschlechtsmerkmale der Teilnehmenden, wie Brustgröße und Entwicklung der Schambehaarung, zugeordnet. Anschließend wurden alle Teilnehmenden entsprechend ihres Tanner-Status in zwei Gruppen eingeteilt: Kinder (Stadium eins bis drei) und Jugendliche (Stadium vier und fünf). Die Differenzierung nach der körperlichen Entwicklung wurde gewählt, da es im Kindesalter erhebliche Veränderungen der TSH- und Schilddrüsenhormonspiegel, insbesondere für fT3, gibt, die mit der Pubertätsreife in Zusammenhang stehen.[48]

Biomarker der Schilddrüsenfunktion

Eine nicht nüchterne Blutprobe wurde während des Termins entnommen und innerhalb von 45 Minuten verarbeitet.[49] TSH, fT3 und fT4 wurden mittels Elektrochemilumineszenz (Elecsys 2010, Roche Diagnostics, Mannheim, Deutschland) im Zentrallabor des Robert Koch Instituts bestimmt. Die interseriellen Variationskoeffizienten (CVs) betrugen 3,9% für TSH, 5,9% für fT3 und 5,3% für fT4. Der Unterschied im medianen Serum-TSH-Spiegel war unabhängig vom Zeitpunkt der Probenentnahme marginal (morgens, 2,11mU/L; nachmittags, 2,12mU/L; abends, 2,31mU/L) und hat die Ergebnisse wahrscheinlich nicht beeinflusst. Erhöhte oder erniedrigte Schilddrüsenhormonwerte wurden anhand alters- und geschlechtsspezifischer Referenzbereiche definiert.[50]

Statistik

Die gesamte Studienpopulation wurde nach Tanner-Status (Kinder und Jugendliche) und dem Vorhandensein einer ADHS-Diagnose oder ADHS-Symptomen stratifiziert, was zu vier verschiedenen Gruppen führte. Kontinuierliche Daten wurden als Median und 25./75. Perzentile (Q1 bzw. Q3) angegeben. Nominale Daten wurden als Gesamtanzahlen und Prozentwerte angegeben. Unterschiede zwischen den Gruppen wurden mittels Kruskal-Wallis

(kontinuierliche Variablen) bzw. X^2-Test (nominale Variablen) berechnet. Assoziationen von TSH, fT3 und fT4 mit der ADHS-Diagnose sowie kategorialen ADHS-Symptomen wurden mit logistischen Regressionsmodellen berechnet, die für Geschlecht, Kindesalter, Geburtsgewicht der Kinder, Rauchverhalten der Mutter während der Schwangerschaft und den aktuellen BMI z-Score des Kindes/Jugendlichen adjustiert wurden. Lineare Regressionsmodelle, die für die gleichen Störfaktoren adjustiert wurden, wurden verwendet, um die Assoziation zwischen TSH, fT3 und fT4 mit kontinuierlichen ADHS-Symptomen zu analysieren. Um potenzielle nichtlineare Beziehungen zu berücksichtigen, wurden potenzielle nicht-lineare Transformationen der Expositions-Variable durch komplexe statistische Methoden wie fractional polynomials oder restricted cubic splines getestet. Dies erlaubt potenzielle nichtlineare Beziehungen von TSH/fT3/fT4 mit der ADHS-Diagnose und Symptomen zu untersuchen. In unseren Analysen fanden wir keine Hinweise auf nichtlineare Zusammenhänge. Ein $p < 0,05$ wurde als statistisch signifikant angesehen. Alle statistischen Analysen wurden in Stata 14 (StataCorp. 2015. College Station, TX, USA) durchgeführt.

Ergebnisse

Tabelle 1 und 2 zeigen die Charakteristika der Studienpopulation stratifiziert nach ADHS-Diagnose und ADHS-Symptomen. In unserer Population wurden insgesamt 420 Kinder und 152 Jugendliche mit ADHS diagnostiziert, während 486 Kinder und 73 Jugendliche ohne vorbekannte ADHS-Diagnose ADHS-Symptome aufwiesen.

Die TSH- und ft4-Konzentrationen waren bei Kindern mit im Vergleich zu Kindern ohne ADHS-Diagnose signifikant niedriger (Tabelle 1). Jugendliche, die entweder eine ADHS-Diagnose oder ADHS-Symptome aufwiesen, hatten im Vergleich zu den Studienteilnehmenden ohne ADHS höhere fT3-Werte. Nur sehr wenige Studienteilnehmende hatten TSH- (n= 58, 0,005%), fT3- (n= 64; 0,006%) oder fT4- (n= 90; 0,008%) Konzentrationen außerhalb des von Kratzsch et al.[50] definierten Referenzbereichs.

Kinder aus den beiden Gruppen, ADHS-Diagnose und ADHS-Symptome, wurden in einer früheren Schwangerschaftswoche geboren, hatten bei der Geburt ein geringeres Gewicht und einen niedrigeren sozioökonomischen Status im Vergleich zu den Kindern ohne ADHS-Diagnose oder -Symptome. Kinder mit einer ADHS-Diagnose hatten einen höheren BMI, während Kinder mit ADHS-Symptomen einen niedrigeren BMI im Vergleich zu den

Studienteilnehmenden ohne ADHS-Symptome hatten. Bei den Jugendlichen waren keine substantiellen Unterschiede für BMI, Gestationswoche, Geburtsgewicht und sozioökonomischen Status zwischen den Gruppen zu beobachten.

Tabelle 1 – Merkmale der Studienpopulation nach ADHS-Diagnosefällen.

	Kinder (Tanner Stadien I – III)				Jugendliche (Tanner Stadien IV – V)			
	ADHS-Diagnose	Keine ADHS-Diagnose	Gesamt	p	ADHS-Diagnose	Keine ADHS-Diagnose	Gesamt	p
n	420	8265	8685		152	2751	2903	
TSH, mIU/L	2.1 (1.6; 3.0)	2.3 (1.7; 3.0)	2.3 (1.7; 3.0)	0.007	1.9 (1.3; 2.7)	1.8 (1.3; 2.5)	1.8 (1.3; 2.5)	0.54
fT3, pmol/L	6.1 (5.7; 6.7)	6.2 (5.7; 6.7)	6.2 (5.7; 6.7)	0.31	5.9 (5.4; 6.7)	5.7 (5.1; 6.3)	5.7 (5.1; 6.3)	0.001
fT4, pmol/L	18.1 (16.4; 19.6)	18.2 (16.8; 19.8)	18.2 (16.7; 19.8)	0.02	17.7 (16.2; 19.4)	18.1 (16.5; 19.9)	18.1 (16.5; 19.9)	0.18
niedriges TSH, n (%)	13 (3.10)	146 (1.77)	159 (1.83)		1 (0.66)	17 (0.62)	18 (0.62)	
hohes TSH, n (%)	6 (1.43)	242 (2.93)	248 (2.86)		10 (6.58)	133 (4.83)	143 (4.93)	
niedriges fT3, n (%)	27 (6.43)	358 (4.33)	385 (4.43)		5 (3.29)	87 (3.16)	92 (3.17)	
hohes fT3, n (%)	11 (2.62)	157 (1.90)	168 (1.93)		3 (1.97)	65 (2.36)	68 (2.34)	
niedriges fT4, n (%)	0 (0)	61 (0.74)	61 (0.70)		1 (0.66)	8 (0.29)	9 (0.31)	
hohes fT4, n (%)	26 (6.19)	878 (10.62)	904 (10.41)		7 (4.61)	221 (8.03)	228 (7.85)	
Männliche Studienteilnehmer (%)	336 (80.0)	4129 (49.96)	4465 (51.41)		120 (78.95)	1272 (46.24)	1392 (47.95)	
Alter, Jahre	10.6 (8.8; 12.5)	8.8 (6.1; 11.5)	9.0 (6.3; 11.6)	< 0.001	15.6 (14.4; 16.7)	15.6 (14.4; 16.7)	15.6 (14.4; 16.7)	0.69
BMI, kg/m^2	17.3 (15.9; 19.6)	16.6 (15.3; 18.9)	16.7 (15.3; 19.0)	< 0.001	21.5 (19.3; 25.2)	21.0 (19.3; 23.4)	21.0 (19.3; 23.5)	0.13
Geburtsgewicht, g	3380 (3000; 3700)	3410 (3080; 3750)	3410 (3080; 3740)	0.03	3370 (3040; 3700)	3380 (3070; 3700)	3380 (3070; 3700)	0.95
<u>Mütterliche Charakteristika</u>								
Schwangerschaftswoche bei Geburt	39 (38; 40)	40 (39; 40)	40 (39; 40)	0.008	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.08
Rauchen während der Schwangerschaft n (%)	95 (23.34)	1321 (16.18)	1416 (16.52)		32 (21.77)	441 (16.28)	473 (16.57)	
Sozialökonomischer Status	10 (8; 13)	11 (9; 15)	11 (9; 15)	< 0.001	11 (8; 14)	11 (9; 15)	11 (8; 15)	0.05

Kontinuierliche Daten ausgedrückt als Median und 25./75. Perzentile; nominale Daten ausgedrückt als Gesamtzahlen und Prozentsätze; Signifikanzniveaus für kontinuierliche Daten wurden mit dem Test auf Differenz im Median bestimmt. [TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; BMI: body mass index].

Tabelle 2 – Merkmale der Studienpopulation nach ADHS-Symptome.

	Kinder (Tanner Stadien I – III)				Jugendliche (Tanner Stadien IV – V)			
	ADHS-Symptome	Keine ADHS-Symptome	Gesamt	p	ADHS-Symptome	Keine ADHS-Symptome	Gesamt	p
n	486	7754	8240		73	2667	2740	
TSH, mIU/L	2.4 (1.8; 3.1)	2.3 (1.7; 3.0)	2.3 (1.7; 3.0)	0.07	1.7 (1.2; 2.3)	1.8 (1.3; 2.5)	1.8 (1.3; 2.5)	0.40
fT3, pmol/L	6.2 (5.7; 6.8)	6.2 (5.7; 6.7)	6.2 (5.7; 6.7)	0.66	6.0 (5.3; 6.7)	5.7 (5.1; 6.3)	5.7 (5.1; 6.3)	0.006
fT4, pmol/L	18.1 (16.7; 19.8)	18.2 (16.8; 19.8)	18.2 (16.8; 19.8)	0.38	17.8 (16.4; 19.6)	18.1 (16.5; 19.9)	18.1 (16.5; 19.9)	0.37
niedriges TSH, n (%)	7 (1.44)	139 (1.79)	146 (1.77)		0 (0)	17 (0.64)	17 (0.62)	
hohes TSH, n (%)	16 (3.29)	226 (2.91)	242 (2.94)		5 (6.85)	127 (4.76)	132 (4.82)	
niedriges fT3, n (%)	16 (3.29)	341 (4.40)	357 (4.33)		1 (1.37)	86 (3.22)	87 (3.18)	
hohes fT3, n (%)	8 (1.65)	148 (1.91)	156 (1.89)		3 (4.11)	61 (2.29)	64 (2.34)	
niedriges fT4, n (%)	3 (0.62)	58 (0.75)	61 (0.74)		0 (0%)	8 (0.30)	8 (0.29)	
hohes fT4, n (%)	47 (9.67)	828 (10.68)	875 (10.62)		6 (8.22)	215 (8.06)	221 (8.07)	
Männliche Studienteilnehmer, n (%)	296 (60.91)	3821 (49.28)	4117 (49.96)		44 (60.27)	1222 (45.82)	1266 (46.20)	
Alter, Jahre	8.2 (5.6; 10.6)	8.9 (6.2; 11.6)	8.8 (6.1; 11.5)	< 0.001	15.0 (14.3; 16.4)	15.6 (14.4; 16.8)	15.6 (14.4; 16.7)	0.04
BMI, kg/m^2	16.4 (15.1; 18.2)	16.7 (15.3; 19.0)	16.6 (15.3; 19.0)	0.007	21.0 (19.2; 23.1)	21.0 (19.3; 23.4)	21.0 (19.3; 23.4)	0.80
Geburtsgewicht, g	3350 (3000; 3650)	3420 (3090; 3750)	3410 (3080; 3750)	0.003	3370 (3020; 3800)	3380 (3070; 3700)	3380 (3070; 3700)	0.92
Mütterliche Charakteristika								
Schwangerschaftswoche bei Geburt	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.03	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.36
Rauchen während der Schwangerschaft, n (%)	143 (29.9)	1175 (15.3)	1318 (16.19)		21 (30.43)	419 (15.94)	440 (16.31)	
Sozialökonomischer Status	10 (7; 12)	11 (9; 15)	11 (9; 15)	< 0.001	11 (8; 13)	11 (9;15)	11 (9;15)	0.09

Kontinuierliche Daten ausgedrückt als Median und 25./75. Perzentile; nominale Daten ausgedrückt als Gesamtzahlen und Prozentsätze; Signifikanzniveaus für kontinuierliche Daten wurden mit dem Test auf Differenz im Median bestimmt [TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; BMI: body mass index].

Die Assoziationen von TSH, fT3 und fT4 im Serum mit ADHS-Diagnose und den ADHS-Symptomen als kategoriale Variable in Tabelle 3 dargestellt. Bei Kindern war eine höhere TSH-Konzentration mit einem geringeren Risiko für eine ADHS-Diagnose assoziiert, allerdings konnten wir weder bei Kindern noch bei Jugendlichen einen Zusammenhang mit ADHS-Symptomen nachweisen. Des Weiteren konnten wir weder bei Kindern noch bei Jugendlichen signifikante Zusammenhänge zwischen fT3 oder fT4 Spiegeln und einer ADHS-Diagnose oder dem Vorhandensein von ADHS-Symptomen zeigen. Bei Betrachtung der ADHS-Symptome als kontinuierliche Variable war fT3 bei Kindern positiv mit ADHS-Symptomen assoziiert (Tabelle 4). Wir fanden keinen statistisch signifikanten Zusammenhang zwischen TSH oder fT4 mit ADHS-Symptomen als kontinuierliche Variable bei Kindern oder Jugendlichen.

Von den Sensitivitätsanalysen schlossen wir alle Kinder und Jugendlichen mit einer bereits diagnostizierten Schilddrüsenstörung sowie diejenigen mit TSH-, fT3- oder fT4-Werten außerhalb des von Kratzsch et al. definierten Referenzbereichs aus.[50] In dieser Untergruppe beobachteten wir keine signifikanten Zusammenhänge von TSH, fT3 oder fT4 mit der ADHS-Diagnose oder –Symptomen (Tabelle **5**). Von einer weiteren Sensitivitätsanalyse schlossen wir alle adipösen Kinder und Jugendlichen aus. Die Assoziation von TSH mit der ADHS-Diagnose bei Kindern war knapp nicht signifikant (p= 0,064), allerdings war die Effektgröße ähnlich derer aus den Hauptanalysen. Auch beim Ausschluss von Kindern mit einem Geburtsgewicht unterhalb der gestationswochenspezifischen zehnten Perzentile änderte sich die Effektgröße für TSH auf die ADHS-Diagnose im Vergleich zur Hauptanalyse nicht, der p-Wert betrug jedoch 0,055. Beim Ausschluss von Kindern, die zu früh geboren wurden, war die Effektgröße für den Zusammenhang zwischen TSH und ADHS-Fällen deutlich geringer als in der Hauptanalyse (OR= 0,93; 95%-CI: 0,83 bis 1,04; p= 0,204). Wir haben auch Interaktionen von TSH, fT3 und fT4 mit dem Geschlecht auf die ADHS-Diagnose und -Symptome getestet; dort allerdings keine signifikanten Interaktionen gefunden (z.B. betrug die Interaktion für TSH-Geschlecht auf die ADHS-Diagnose p= 0,759 bei Kindern und p= 0,595 bei Jugendlichen).

Tabelle 3 – Ergebnisse der logistischen Regressionsanalyse zwischen den Biomarkern der Schilddrüsenfunktion und der ADHS-Diagnose sowie den ADHS-Symptomen.

	ADHS-Diagnose (J/N)		ADHS-Symptome (J/N)	
	Kinder (Tanner I-III)	Jugendliche (Tanner IV-V)	Kinder (Tanner I-III)	Jugendliche (Tanner IV-V)
	OR (KI)	OR (KI)	OR (KI)	OR (KI)
TSH, mIU/L	0.90 (0.81; 1.00)*	1.05 (0.90; 1.23)	1.00 (1.00; 1.01)	1.00 (0.78; 1.28)
fT3, pmol/L	1.00 (0.88; 1.12)	1.03 (0.81; 1.30)	1.02 (0.92; 1.14)	1.16 (0.89; 1.51)
fT4, pmol/L	0.96 (0.91; 1.01)	0.94 (0.86; 1.03)	0.97 (0.92; 1.02)	0.99 (0.90; 1.09)

Dargestellt sind bereinigte Odds Ratios (OR) mit 95% Konfidenzintervall (KI). Die Modelle wurden für Geschlecht, Alter und Gewicht bei der Geburt sowie für die folgenden Kovariaten angepasst: Rauchgewohnheiten der Mutter während der Schwangerschaft und der aktuelle BMI-Z-Score des Kindes/Jugendlichen [TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine] *p≤0.05

Tabelle 4 – Ergebnisse der linearen Regressionsanalyse zur Assoziation von Biomarkern der Schilddrüsenfunktion und ADHS Symptomen.

	Kontinuierlicher SDQ- Subskalenwert zu ADHS-Symptome	
	Kinder (Tanner I-III)	Jugendliche (Tanner IV-V)
	β (CI)	β (CI)
TSH	0.00 (-0.03; 0.04)	0.03 (-0.10; 0.04)
fT3	0.08 (0.03; 0.14)*	0.07 (-0.02; 0.16)
fT4	-0.02 (-0.04; 0.00)	-0.02 (-0.06; 0.01)

Dargestellt sind bereinigte β Schätzer mit 95% Konfidenzintervall (KI). Die Modelle wurden für Geschlecht, Alter und Gewicht bei der Geburt sowie für die folgenden Kovariaten angepasst: Rauchgewohnheiten der Mutter während der Schwangerschaft und der aktuelle BMI-Z-Score des Kindes/Jugendlichen [TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine] *p≤0.05

Tabelle 5 – Ergebnisse der logistischen Regressionsanalyse zur Assoziation von Biomarkern (alters- und geschlechtsadjustierte Referenzintervalle 2,5. und 97,5 Perzentil)[50] der Schilddrüsenfunktion und der ADHS-Diagnose sowie den ADHS-Symptomen.

	ADHS-Diagnose (J/N)				ADHS-Symptome (J/N)			
	Kinder (Tanner I-III)		Jugendliche (Tanner IV-V)		Kinder (Tanner I-III)		Jugendliche (Tanner IV-V)	
	N	OR (KI)	N	OR (KI)	N	OR (KI)	N	OR (KI)
TSH < 2,5 Perzentil	13	1.04 (0.53; 2.02)	1	2.21 (0.25; 19.68)	7	0.45 (0.15; 1.35)	0	-
TSH > 97,5 Perzentil	6	0.32 (0.10; 0.98)	10	1.27 (0.58; 2.78)	16	1.07 (0.58; 1.98)	5	1.12 (0.40; 3.15)
fT3 < 2,5 Perzentil	27	1.39 (0.87; 2.23)	5	2.42 (0.88; 6.66)	16	0.59 (0.34; 1.03)	1	0.23 (0.03; 1.75)
fT3 > 97,5 Perzentil	11	0.55 (0.23; 1.34)	3	0.52 (0.14; 1.88)	8	0.76 (0.34; 1.69)	3	1.77 (0.52; 6.08)
fT4 < 2,5 Perzentil	0	-	1	-	3	1.47 (0.36; 6.05)	0	-
fT4 > 97,5 Perzentil	26	0.73 (0.45; 1.20)	7	0.49 (0.18; 1.31)	47	0.93 (0.61; 1.44)	6	0.99 (0.41; 2.44)

Dargestellt sind bereinigte Odds Ratios (OR) mit 95% Konfidenzintervall (KI). Die Modelle wurden für Geschlecht, Alter und Gewicht bei der Geburt sowie für die folgenden Kovariaten angepasst: Rauchgewohnheiten der Mutter während der Schwangerschaft und der aktuelle BMI-Z-Score des Kindes/Jugendlichen [TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine] *p≤0.05

Diskussion

In der vorliegenden Studie wurde untersucht, ob Biomarker der Schilddrüsenfunktion bei Kindern und Jugendlichen mit der Diagnose oder Symptomatik von ADHS assoziiert sind. Wir konnten zeigen, dass eine niedrigere TSH-Konzentration im Serum mit einem erhöhten Risiko für eine ADHS-Diagnose bei Kindern, aber nicht bei Jugendlichen assoziiert war. Bei der Analyse der ADHS-Symptome als kontinuierliche Variable war fT3 positiv mit den ADHS-Symptomen bei Kindern assoziiert. Für fT4 wurde kein Zusammenhang mit einer ADHS-Diagnose oder ADHS-Symptomen bei Kindern oder Jugendlichen gefunden. Insgesamt unterstützen unsere Ergebnisse die Vermutung, dass ein niedrigerer TSH-Spiegel mit einem höheren Risiko für ADHS bei Kindern, aber nicht bei Jugendlichen assoziiert ist.

Einordnung der Ergebnisse in die Literatur

Unsere Ergebnisse stimmen mit aktuellen Arbeiten von Villanger et al. überein, die berichteten, dass das ADHS-Risiko bei Neugeborenen mit niedrigen TSH-Werten erhöht ist, nachdem sie TSH-Konzentrationen unter 10 mU/L bei 405 ADHS-Fällen und 1.092 Kontrollen analysierten.[51]

Die Schilddrüsenfunktion kann entweder direkt durch die Messung der Schilddrüsenhormone (fT3, fT4) oder indirekt durch die Bestimmung der TSH-Konzentration charakterisiert werden. Da die TSH Konzentration im Serum in einem umgekehrten log-linearen Verhältnis zu fT4 steht, kann eine geringe Veränderung im fT4-Spiegel eine proportional viel stärkere Regulierung der TSH Konzentration bewirken.[27] Daher könnte die TSH-Messung im Serum eine bessere Sensitivität für den Nachweis einer Schilddrüsendysfunktion bieten als die Messung von fT3 und fT4. Dies ist besonders relevant im Hinblick auf unsere Ergebnisse bezüglich der positiven Assoziation zwischen TSH und der ADHS-Diagnose bei Kindern.

Frühere Befunde deuten darauf hin, dass die Schilddrüsenfunktion für die Entwicklung des Gehirns von zentraler Bedeutung ist.[52-55] Da dies für alle Stadien der Gehirnentwicklung gilt, ist die mütterliche Schilddrüsenfunktion für die frühe Gehirnentwicklung wichtig, während die kindliche Schilddrüsenfunktion für die späteren Stadien der Gehirnreifung wesentlich ist.[56, 57] Unsere Analyse zeigte, dass, obwohl die Prävalenz der ADHS-Diagnose bei Kindern und Jugendlichen ungefähr gleich ist, die Schilddrüsenhormone unterschiedlich sind. Bei Kindern mit

einer ADHS-Diagnose waren TSH und fT4 Konzentration im Mittel niedriger als bei Kindern ohne ADHS-Diagnose. Bei Jugendlichen, die entweder eine ADHS-Diagnose oder ADHS-Symptome hatten, waren die fT3 Konzentrationen im Mittel höher als bei jenen ohne ADHS-Diagnose oder Symptomen. Daher könnten niedrige TSH und hohe fT3 Konzentrationen das Risiko für ADHS erhöhen.

In unserer Kohorte war eine um 1 mIU/l niedrigere TSH Konzentration im Serum mit einem um 10% höheren Risiko für eine bekannte ADHS-Diagnose bei Kindern verbunden. Dieses Ergebnis könnte die Bedeutung von TSH während der frühen Gehirnentwicklung unterstützen, da diese Assoziationen im Kindes-, aber nicht im Jugendalter gefunden wurden. Da wir außerdem keine signifikanten Zusammenhänge zwischen TSH und fT4 mit ADHS-Symptomen fanden, deuten unsere Ergebnisse darauf hin, dass diese Parameter möglicherweise nicht für die ADHS-Diagnose bei Heranwachsenden geeignet sind. Darüber hinaus ist zu beachten, dass die positive Assoziation von fT3 mit ADHS-Symptomen (Tabelle 4) möglicherweise einfach ein Ergebnis für das Unaufmerksamkeits- und Hyperaktivitätsverhalten der Kinder an der oberen Grenze der physiologischen Variation ist.

Von unserer Studie haben wir insgesamt 224 Kinder und Jugendliche mit Schilddrüsenmedikation von unserer Analyse ausgeschlossen, da sich sowohl die Schilddrüsenfunktion und die ADHS-Symptome seit Beginn der Medikation deutlich verändert haben könnten. Somit wäre es schwierig, den Einfluss der aktuellen Schilddrüsenfunktion zu beurteilen, wenn diese Studienteilnehmende Schilddrüsenmedikamente einnehmen.

Limitationen der Analyse

Diese Untersuchung hat mehrere Einschränkungen. Erstens wurde die ADHS-Diagnose von den Eltern nach einer vorherigen Diagnose durch einen Arzt oder Psychologen mitgeteilt. Das Alter der Kinder/Jugendlichen zum Zeitpunkt der Diagnose ist unbekannt. Um die Entscheidungsfindung zur Diagnose von ADHS zu unterstützen sollen laut Leitlinie Multi-Informanten-Ratingskalen eingesetzt werden.[58, 2] Die Erhebung zusätzlicher Informationen von Lehrern und/oder Verwandten war in dieser Kohortenstudie mit mehr als 10.000 Teilnehmenden nicht praktikabel. Zweitens wurde die Verwendung von stimulierenden Medikamenten (z.B. Methylphenidat) bei Teilnehmenden mit einer ADHS-Diagnose im Fragebogen nicht erfasst. Eine Methylphenidat-Behandlung hatte jedoch keine nachhaltigen Auswirkungen auf die Schilddrüsenfunktion bei vorpubertären Kindern mit ADHS.[59] Drittens, obwohl sowohl Hypo- als

auch Hyperthyreose bei Müttern während der Schwangerschaft mit einem erhöhten Risiko für ADHS bei Kindern in Verbindung gebracht wurden, enthielt die Kohorte keine Informationen zum Schilddrüsenstatus der Mutter während der Schwangerschaft. Eine Meta-Analyse von Studien mit longitudinaler Nachbeobachtung von Kindern mit ADHS bis zum Erwachsenenalter (25 Jahren) deutete darauf hin, dass bei 35% der Kinder die ADHS-Symptome verschwanden, während 50% die Kriterien für ADHS in partieller Remission erfüllten und 15% weiterhin die vollen diagnostischen Kriterien für ADHS erfüllten.[5, 60] Unsere Querschnittsanalyse kann die aktuelle ADHS-Diagnose nicht mit der ADHS im Erwachsenenalter in Verbindung bringen, daher muss eine longitudinale Analyse bewerten, wann und wie eine Schilddrüsenfehlfunktion zur Pathophysiologie der ADHS beitragen kann.

Nichtsdestotrotz hat diese Analyse auch einige Stärken. Unsere Studienpopulation bestand aus einer sehr großen Kohorte von Kindern und Jugendlichen (n> 10.000), die repräsentativ für die deutsche Jugend war. Insbesondere waren die Informationen zu zahlreichen potentiellen Störfaktoren verfügbar. Zur Erfassung der ADHS-Symptomatik der Teilnehmenden im Alter von 3 bis 11 Jahren wurde zusätzlich zum SDQ-Score des Elternfragebogens eine Verhaltensbeurteilung bei der ärztlichen Untersuchung durchgeführt. Außerdem wurden in einem Zentrallabor altersspezifisch und hochstandardisiert TSH, fT3, fT4 gemessen.

Fazit der Studie

Die vielfältigen kurz- und langfristigen medizinischen, sozialen und gesundheitsökonomischen Folgen von ADHS verdeutlichen die hohe Public-Health-Relevanz dieser Störung. Dennoch sind die Möglichkeiten der Primärprävention aufgrund des hohen Anteils genetischer Faktoren an der Ätiologie von ADHS begrenzt. Die Assoziation von Schilddrüsenfehlfunktionen mit neurologischen und psychischen Auffälligkeiten war schon immer von besonderem Interesse, da das Gehirn ein Zielorgan für Schilddrüsenhormone ist und selbst kleine individuelle Unterschiede große Konsequenzen für die öffentliche Gesundheit haben können.[61] Die gezeigte Assoziation zwischen TSH und der ADHS-Diagnose bei Kindern im Rahmen der KiGGS-Baseline-Studie unterstreicht die Notwendigkeit weiterer Studien zur Erforschung der Rolle von Schilddrüsenhormonen und ADHS bei Kindern und Jugendlichen. Die altersspezifischen Befunde (d.h. signifikante Assoziationen bei Kindern, aber nicht bei Jugendlichen) deuten darauf hin, dass der Einfluss der Schilddrüse auf die ADHS altersabhängig und besonders in den frühen Lebensjahren von Relevanz ist. Diese Informationen könnten in Zukunft zu einer ADHS-

Therapie führen, die sowohl chronologisches und biologisches Alter, als auch Symptomschwere beinhaltet und somit einen personalisierten Ansatz verfolgt.

Literaturverzeichnis

1. Getahun D, Jacobsen SJ, Fassett MJ, Chen W, Demissie K, Rhoads GG. Recent trends in childhood attention-deficit/hyperactivity disorder. JAMA pediatrics 2013;167(3):282-288.
2. American Psychiatric Association A. Diagnostic and statistical manual of mental disorders: American Psychiatric Publishing; 2013.
3. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics 2015;135(4):e994-e1001.
4. Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. American journal of psychiatry 2007;164(6):942-948.
5. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychological medicine 2006;36(2):159-165.
6. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Human genetics 2009;126(1):51-90.
7. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med 2006;36(2):159-65.
8. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD? Journal of Child Psychology and Psychiatry 2013;54(1):3-16.
9. Wang L-J, Huang Y-H, Chou W-J, Lee S-Y, Chang H-Y, Chen C-C, Chao H-R. Interrelationships among growth hormone, thyroid function, and endocrine-disrupting chemicals on the susceptibility to attention-deficit/hyperactivity disorder. European Child & Adolescent Psychiatry 2022.
10. Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. Journal of the American Academy of Child & Adolescent Psychiatry 2012;51(1):86-97. e8.
11. Gustavson K, Ystrom E, Stoltenberg C, Susser E, Surén P, Magnus P, Knudsen GP, Smith GD, Langley K, Rutter M. Smoking in pregnancy and child ADHD. Pediatrics 2017;139(2).
12. Huang L, Wang Y, Zhang L, Zheng Z, Zhu T, Qu Y, Mu D. Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Pediatrics 2018;141(1):e20172465.
13. Andersen SL, Andersen S, Vestergaard P, Olsen J. Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: A Danish nationwide case-cohort study. Thyroid 2018;28(4):537-546.
14. Andersen SL, Laurberg P, Wu C, Olsen J. Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a D anish nationwide cohort study. BJOG: An International Journal of Obstetrics & Gynaecology 2014;121(11):1365-1374.
15. Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, de Muinck Keizer-Schrama SM, Hooijkaas H, Steegers EA, Hofman A. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatric research 2011;69(5, Part 1 of 2):454.
16. Ghassabian A, Bongers-Schokking JJ, De Rijke YB, Van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. Thyroid 2012;22(2):178-186.
17. Zimmermann MB. Iodine deficiency. Endocrine reviews 2009;30(4):376-408.
18. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet 2013;382(9889):331-337.
19. Drover SS, Villanger GD, Aase H, Skogheim TS, Longnecker MP, Zoeller RT, Reichborn-Kjennerud T, Knudsen GP, Zeiner P, Engel SM. Maternal thyroid function during pregnancy or

neonatal thyroid function and attention deficit hyperactivity disorder: A systematic review. Epidemiology (Cambridge, Mass) 2019;30(1):130.
20. Abel MH, Ystrom E, Caspersen IH, Meltzer HM, Aase H, Torheim LE, Askeland RB, Reichborn-Kjennerud T, Brantsæter AL. Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study. Nutrients 2017;9(11).
21. Ittermann T, Albrecht D, Arohonka P, Bilek R, de Castro JJ, Dahl L, Filipsson Nystrom H, Gaberscek S, Garcia-Fuentes E, Gheorghiu ML, Hubalewska-Dydejczyk A, Hunziker S, Jukic T, Karanfilski B, Koskinen S, Kusic Z, Majstorov V, Makris KC, Markou KB, Meisinger C, Milevska Kostova N, Mullen KR, Nagy EV, Pirags V, Rojo-Martinez G, Samardzic M, Saranac L, Strele I, Thamm M, Top I, Trofimiuk-Müldner M, Ünal B, Koskinen S, Vila L, Vitti P, Winter B, Woodside JV, Zaletel K, Zamrazil V, Zimmermann M, Erlund I, Völzke H. Standardized Map of Iodine Status in Europe. Thyroid 2020;30(9):1346-1354.
22. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018;14(5):301-316.
23. Constant E, De Volder A, Ivanoiu A, Bol A, Labar D, Seghers A, Cosnard G, Melin J, Daumerie C. Cerebral blood flow and glucose metabolism in hypothyroidism: a positron emission tomography study. The Journal of Clinical Endocrinology & Metabolism 2001;86(8):3864-3870.
24. Bauer M, Goetz T, Glenn T, Whybrow P. The thyroid-brain interaction in thyroid disorders and mood disorders. Journal of neuroendocrinology 2008;20(10):1101-1114.
25. Ahmed OM, El-Gareib A, El-Bakry A, Abd El-Tawab S, Ahmed R. Thyroid hormones states and brain development interactions. International Journal of Developmental Neuroscience 2008;26(2):147-209.
26. Zader SJ, Williams E, Buryk MA. Mental health conditions and hyperthyroidism. Pediatrics 2019;144(5).
27. Álvarez-Pedrerol M, Ribas-Fitó N, Torrent M, Julvez J, Ferrer C, Sunyer J. TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. Clinical endocrinology 2007;66(6):890-898.
28. Valentine J, Rossi E, O'LEARY P, Parry T, Kurinczuk J, Sly P. Thyroid function in a population of children with attention deficit hyperactivity disorder. Journal of paediatrics and child health 1997;33(2):117-120.
29. Weiss RE, Stein MA, Trommer B, Refetoff S. Attention-deficit hyperactivity disorder and thyroid function. The Journal of pediatrics 1993;123(4):539-545.
30. Spencer T, Biederman J, Wilens T, Guite J, Harding M. ADHD and thyroid abnormalities: a research note. Journal of Child Psychology and Psychiatry 1995;36(5):879-885.
31. May T, Adesina I, McGillivray J, Rinehart NJ. Sex differences in neurodevelopmental disorders. Current opinion in neurology 2019;32(4):622-626.
32. Murray AL, Booth T, Eisner M, Auyeung B, Murray G, Ribeaud D. Sex differences in ADHD trajectories across childhood and adolescence. Developmental science 2019;22(1):e12721.
33. Cortese S, Moreira-Maia CR, St. Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association between ADHD and obesity: a systematic review and meta-analysis. American Journal of Psychiatry 2016;173(1):34-43.
34. Nigg JT, Johnstone JM, Musser ED, Long HG, Willoughby MT, Shannon J. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. Clinical psychology review 2016;43:67-79.
35. Ask H, Gustavson K, Ystrom E, Havdahl KA, Tesli M, Askeland RB, Reichborn-Kjennerud T. Association of gestational age at birth with symptoms of attention-deficit/hyperactivity disorder in children. JAMA pediatrics 2018;172(8):749-756.
36. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, Procianoy RS, Rohde LA, Moreira-Maia CR. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics 2018;141(1).
37. Soneji S, Beltrán-Sánchez H. Association of maternal cigarette smoking and smoking cessation with preterm birth. JAMA network open 2019;2(4):e192514-e192514.
38. Inoue S, Naruse H, Yorifuji T, Kato T, Murakoshi T, Doi H, Subramanian S. Impact of maternal and paternal smoking on birth outcomes. Journal of Public Health 2017;39(3):1-10.

39. Kurth B-M, Kamtsiuris P, Hölling H, Schlaud M, Dölle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink GB. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. BMC Public health 2008;8(1):1-8.
40. Kurth B-M, Kamtsiuris P, Hölling H, Schlaud M, Dölle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink G. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. BMC Public health 2008;8(1):1-8.
41. Winkler J, Stolzenberg H. Social class index in the Federal Health Survey. Gesundheitswesen (Bundesverband Der Arzte Des Offentlichen Gesundheitsdienstes (Germany) 1999;61:S178-83.
42. Organization WH. International statistical classification of diseases and related health problems: 10th revision (ICD-10). http://www who int/classifications/apps/icd/icd 1992.
43. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. Journal of the American Academy of Child & Adolescent Psychiatry 2001;40(11):1337-1345.
44. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. The British journal of psychiatry 2000;177(6):534-539.
45. Woerner W, Becker A, Rothenberger A. Normative data and scale properties of the German parent SDQ. European child & adolescent psychiatry 2004;13(2):ii3-ii10.
46. Hölling H, Erhart M, Ravens-Sieberer U, Schlack R. Verhaltensauffälligkeiten bei kindern und jugendlichen. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz 2007;50(5):784-793.
47. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Archives of disease in childhood 1976;51(3):170-179.
48. Taylor PN, Sayers A, Okosieme O, Das G, Draman MS, Tabasum A, Abusahmin H, Rahman M, Stevenson K, Groom A. Maturation in serum thyroid function parameters over childhood and puberty: results of a longitudinal study. The Journal of Clinical Endocrinology & Metabolism 2017;102(7):2508-2515.
49. Thierfelder W, Dortschy R, Hintzpeter B, Kahl H, Scheidt-Nave C. Biochemical measures in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2007;50(5-6):757-770.
50. Kratzsch J, Schubert G, Pulzer F, Pfaeffle R, Koerner A, Dietz A, Rauh M, Kiess W, Thiery J. Reference intervals for TSH and thyroid hormones are mainly affected by age, body mass index and number of blood leucocytes, but hardly by gender and thyroid autoantibodies during the first decades of life. Clinical biochemistry 2008;41(13):1091-1098.
51. Villanger GD, Ystrom E, Engel SM, Longnecker MP, Pettersen R, Rowe AD, Reichborn-Kjennerud T, Aase H. Neonatal thyroid-stimulating hormone and association with attention-deficit/hyperactivity disorder. Paediatric and Perinatal Epidemiology 2020.
52. Päkkilä F, Männistö T, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Vääräsmäki M, Järvelin MR, Moilanen I, Suvanto E. The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child. J Clin Endocrinol Metab 2014;99(1):E1-8.
53. Chevrier J, Harley KG, Kogut K, Holland N, Johnson C, Eskenazi B. Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age. J Thyroid Res 2011;2011:426427.
54. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 2004;89(12):6054-60.
55. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341(8):549-55.
56. Rovet JF. The role of thyroid hormones for brain development and cognitive function. In: Paediatric Thyroidology: Karger Publishers; 2014. p. 26-43.
57. Bernal J. Thyroid hormone receptors in brain development and function. Nature Reviews Endocrinology 2007;3(3):249.
58. De Los Reyes A, Augenstein TM, Wang M, Thomas SA, Drabick DA, Burgers DE, Rabinowitz J. The validity of the multi-informant approach to assessing child and adolescent mental health. Psychological bulletin 2015;141(4):858.

59. Bereket A, Turan S, Karaman MG, Haklar G, Ozbay F, Yazgan MY. Height, weight, IGF-I, IGFBP-3 and thyroid functions in prepubertal children with attention deficit hyperactivity disorder: effect of methylphenidate treatment. Hormone Research in Paediatrics 2005;63(4):159-164.
60. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. Journal of the American Academy of Child Psychiatry 1985;24(2):211-220.
61. Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. The Journal of Clinical Endocrinology & Metabolism 2015;100(4):1256-1266.

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Anhang

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The association between thyroid function biomarkers and attention deficit hyperactivity disorder

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The relation between thyroid function biomarkers and attention deficit hyperactivity disorder (ADHD) in children and adolescents is currently unclear. Cross-sectional data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Baseline) was analyzed to assess the association between thyroid function biomarkers and ADHD in a population-based, nationally representative sample. The study cohort included 11,588 children and adolescents with 572 and 559 having an ADHD diagnosis or symptoms, respectively. ADHD symptoms were assessed through the *Inattention/Hyperactivity* subscale of the Strength and Difficulties Questionnaire. ADHD diagnosis was determined by a physician or psychologist. Serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) concentrations were determined enzymatically. Adjusted regression models were used to relate serum TSH, fT3, and fT4 with risk for ADHD diagnosis or symptoms. In children, a 1 mIU/l higher TSH was related to a 10% lower risk (odds ratio [OR] 0.90; 95% confidence interval [CI] 0.81–1.00) of ADHD diagnosis. We found a significant positive association between fT3 and continuously assessed ADHD symptoms in children (β 0.08; 95% CI 0.03–0.14). Our results suggest that physical maturity may influence the association between thyroid function biomarkers and risk for ADHD.

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and is showing an increasing prevalence[1]. Symptoms are characterized by difficulties with concentration and attention, with controlling behavior, and hyperactivity[2]. ADHD affects approximately 7.1% of children and adolescents worldwide[3] exceeding previous estimates of 5.3%[4], and persists into adulthood in 65% of cases[5].

ADHD shows considerable clinical heterogeneity in terms of symptom severity, admixture of symptoms, developmental course, and comorbidities. These parameters are influenced by inherited and non-inherited factors. Genetic variants (i.e. single nucleotide polymorphisms) are likely to be involved in the pathophysiology of ADHD[6]. However, their effect sizes are rather small. Interestingly, twin and adoption studies[7–9] found a high mean heritability of 0.77. Endocrine disorders also influence ADHD susceptibility. Specifically, environmental toxins in-utero or early childhood such as exposure to lead, organophosphate pesticides, and polychlorinated biphenyls are risk factors for ADHD[10]. ADHD susceptibility is not influenced by nutritional deficiencies, nutritional surpluses (e.g. sugar and artificial food colorings), and low or high Immunoglobulin G (IgG) foods[11]. Further evidence suggests that there is no causal association between maternal smoking during pregnancy and offspring ADHD[12]. While a recent meta-analysis provided evidence for an association between maternal smoking and offspring ADHD [13], the authors also reported significant heterogeneity between studies ($I^2 = 79.2\%$, $p < 0.01$).

Maternal thyroid dysfunction may adversely affect fetal brain development. Maternal (overt) hyperthyroidism[14,15], high thyroid stimulating hormone (TSH) concentration during pregnancy[16], and maternal autoimmune thyroiditis[17] in early pregnancy increase the offspring's risk for ADHD. Though there is an association between maternal thyroid dysfunction and offspring ADHD[18], the knowledge on the association between iodine intake in pregnancy and offspring's risk of diagnosed ADHD is sparse. A large Norwegian cohort study did not find a significant association with maternal iodine intake and child ADHD diagnosis but with symptoms[19].

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This is supported by a large Danish cohort study. Inadequate maternal iodine intake and increased risk of ADHD symptoms in children is suggested by previous research[14].

As synthesis and secretion of thyroid hormones are regulated by a negative feedback system that involves the hypothalamus, pituitary and thyroid gland (the HPT axis)[20], thyroid function becomes important for the cognitive development in children and adolescents[21]. As individuals with hyperthyroidism may have ADHD-like symptoms (e.g. anxiety, nervousness, irritability, and physical hyperactivity)[22], several studies investigated the association between thyroid dysfunction and ADHD in children. Zader et al. concluded that children with hyperthyroidism have an ADHD prevalence ratio of 1.7 compared to children without hyperthyroidism. Even more notably, in 40% of cases, the mental health diagnosis antedated the hyperthyroidism by 90 days, with ADHD being diagnosed before hyperthyroidism in 68.3% of cases[23]. Even within the normal range, TSH concentrations in the upper quartile were positively associated with ADHD symptoms in healthy children[24]. In adolescents, on the other hand, thyroid disorders were not related with ADHD[25]. Early studies with clinically referred ADHD children and adolescents were inconclusive with regards to thyroid dysfunction. Some supported a link between thyroid function abnormalities and the cognitive-behavioral manifestations of ADHD[26], while others did not[27]. Hence, previous investigations showed large heterogeneity, which may be partly due to the relatively small sample sizes between 150[25,27] and 350[24,26] evaluated ADHD cases.

We associated TSH and circulating thyroid hormones with the risk of ADHD using cross-sectional data from the large-scale population-based German Health Interview and Examination Survey for Children and Adolescents (KiGGS Baseline). Specifically, we investigated first how serum TSH, free triiodothyronine (fT3), and free thyroxine (fT4) were related to ADHD symptoms as well as ADHD diagnosis. We adjusted our regression models with several covariates previously identified in the literature to be associated with thyroid function and ADHD. We included sex since male children are three times more likely to have ADHD compared to female children. In adulthood men and women are equally likely to have ADHD[28]. In line with this finding, recent research suggested that changes in the symptom profile of ADHD, with hyperactivity emerging in childhood for males but having later onset at the time of adolescence for females, may contribute to this pattern[29]. We also included body mass index (BMI) because previous meta-analyses found a positive association between ADHD and overweight or, in extreme cases, obesity[30,31]. ADHD has also been found to be associated significantly with low birth weight and prematurity in several cohort studies and meta-analyses[32,33]. Since maternal smoking is a risk factor for lower birth weight and preterm birth[34,35], this covariate was also used along with weight at birth in our regression analysis. In summary, for our regression analysis we included offspring's sex and birth weight, age, BMI and maternal smoking as covariates.

Results

Tables 1 and 2 show the characteristics of the study population stratified by ADHD diagnosis and ADHD symptoms. In our population a total of 420 children and 152 adolescents were diagnosed with ADHD while 486 children and 73 adolescents showed ADHD symptoms.

TSH and ft4 concentrations were significantly lower in children with compared to children without ADHD diagnosis (Table 1). Adolescents with either ADHD diagnosis or ADHD symptoms had higher fT3 levels compared to controls. Very few study participants had TSH (n = 58, 0.005%), fT3 (n = 74; 0.006%) and fT4 (n = 90; 0.008%) concentrations outside the reference range defined by Kratzsch et al[36].

Children in both groups, ADHD diagnosis and ADHD symptoms, were born during an earlier gestational week, weighted less at birth and had a lower socioeconomic status compared to controls. Children with an ADHD diagnosis had a higher BMI while children with ADHD symptoms had a lower BMI compared to controls. In adolescents no differences for BMI, gestational week of birth, birth weight and socioeconomic status were found.

The association of serum TSH, fT3 and fT4 for both groups, ADHD diagnosis and ADHD symptoms as categorical variable, is presented in Table 3. In children, a higher TSH concentration was associated with a lower risk for ADHD diagnosis. TSH was not related to ADHD symptoms in children or adolescents. Further, fT3 or fT4 were not significantly associated with ADHD diagnosis and ADHD symptoms as a categorical variable for neither children nor adults. When looking at ADHD symptoms as a continuous variable, fT3 was positively associated with ADHD symptoms in children (Table 4). We found no statistically significant relationship between TSH or fT4 with ADHD symptoms as a continuous variable for children or adolescents.

For sensitivity analyses, we excluded all children and adolescents with an already diagnosed thyroid disorder as well as those with TSH, fT3 or fT4 values outside the reference range as defined by Kratzsch et al.[36] In this subgroup, we observed no significant associations of TSH, fT3 or fT4 with ADHD diagnosis or symptoms. In another sensitivity analysis, we excluded all obese children and adolescents. Here we found a strong trend for the association between TSH with ADHD diagnosis in children ($p = 0.064$). However, the effect size was similar to the one of the main analyses. Likewise, when excluding children with a birthweight below the gestational week specific 10th percentile the effect size for TSH on ADHD diagnosis did not change compared to the main analysis, but the p-value was 0.055. When excluding children born preterm, the effect size for the association between TSH and ADHD cases was markedly lower than in the main analysis (OR 0.93; 95% CI 0.83–1.04; $p = 0.204$). We have also tested interactions of TSH, fT3 and fT4 with sex on ADHD diagnosis and symptoms; however, we did not find any significant interactions (e.g. interactions for TSH-sex on ADH diagnosis was 0.759 in children and 0.595 in adolescents).

Discussion

The present study investigated whether thyroid function biomarkers of children and adolescents are associated with ADHD diagnosis or symptoms. We demonstrated that higher serum TSH levels were associated with a lower risk for ADHD diagnosis in children but not adolescents. When analyzing ADHD symptoms as a continuous

	Children (tanner stage I–III)				Adolescents (tanner stage IV–V)			
	ADHD diagnosis	Control	Total	*p*	ADHD diagnosis	Control	Total	*p*
n	420	8265	8685		152	2751	2903	
TSH, mIU/L	2.1 (1.6; 3.0)	2.3 (1.7; 3.0)	2.3 (1.7; 3.0)	0.007	1.9 (1.3; 2.7)	1.8 (1.3; 2.5)	1.8 (1.3; 2.5)	0.54
fT3, pmol/L	6.1 (5.7; 6.7)	6.2 (5.7; 6.7)	6.2 (5.7; 6.7)	0.31	5.9 (5.4; 6.7)	5.7 (5.1; 6.3)	5.7 (5.1; 6.3)	0.001
fT4, pmol/L	18.1 (16.4; 19.6)	18.2 (16.8; 19.8)	18.2 (16.7; 19.8)	0.02	17.7 (16.2; 19.4)	18.1 (16.5; 19.9)	18.1 (16.5; 19.9)	0.18
Low TSH[a], n (%)	13 (3.10)	146 (1.77)	159 (1.83)		1 (0.66)	17 (0.62)	18 (0.62)	
High TSH[a], n (%)	6 (1.43)	242 (2.93)	248 (2.86)		10 (6.58)	133 (4.83)	143 (4.93)	
Low fT3 [a], n (%)	27 (6.43)	358 (4.33)	385 (4.43)		5 (3.29)	87 (3.16)	92 (3.17)	
High fT3[a], n (%)	11 (2.62)	157 (1.90)	168 (1.93)		3 (1.97)	65 (2.36)	68 (2.34)	
Low fT4[a], n (%)	0 (0)	61 (0.74)	61 (0.70)		1 (0.66)	8 (0.29)	9 (0.31)	
High fT4[a], n (%)	26 (6.19)	878 (10.62)	904 (10.41)		7 (4.61)	221 (8.03)	228 (7.85)	
Males	336 (80.0)	4129 (49.96)	4465 (51.41)		120 (78.95)	1272 (46.24)	1392 (47.95)	
Age, years	10.6 (8.8; 12.5)	8.8 (6.1; 11.5)	9.0 (6.3; 11.6)	< 0.001	15.6 (14.4; 16.7)	15.6 (14.4; 16.7)	15.6 (14.4; 16.7)	0.69
BMI, kg/m^2	17.3 (15.9; 19.6)	16.6 (15.3; 18.9)	16.7 (15.3; 19.0)	< 0.001	21.5 (19.3; 25.2)	21.0 (19.3; 23.4)	21.0 (19.3; 23.5)	0.13
Weight at birth, g	3380 (3000; 3700)	3410 (3080; 3750)	3410 (3080; 3740)	0.03	3370 (3040; 3700)	3380 (3070; 3700)	3380 (3070; 3700)	0.95
Maternal characteristics								
Gestational week at birth	39 (38; 40)	40 (39; 40)	40 (39; 40)	0.008	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.08
Gestational smoking n (%)	95 (23.34)	1321 (16.18)	1416 (16.52)		32 (21.77)	441 (16.28)	473 (16.57)	
Socioeconomic status	10 (8; 13)	11 (9; 15)	11 (9; 15)	< 0.001	11 (8; 14)	11 (9; 15)	11 (8; 15)	0.05

Table 1. Characteristics of the study population by ADHD diagnosis cases. Continuous data expressed as median and 25th/75th percentiles; nominal data expressed as total numbers and percentages; significance levels for continuous data was determined with the test for difference in median. *TSH* thyroid stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxine, *BMI* body mass index. [a]Defined according to Kratzsch et al[36].

variable, fT3 was positively associated with ADHD symptoms in children. No relationship was found for fT4 with an ADHD diagnosis or ADHD symptoms in children or adolescents. Overall, our results support the notion that lower serum TSH may be related to a higher risk for ADHD in children but not adolescents. These findings agree with recent work by Villanger et al. who reported that ADHD risk appeared to be elevated among newborns with low TSH levels after analyzing TSH concentrations below 10 mIU/L in 405 ADHD cases and 1092 controls[37].

Thyroid function can be determined either directly, by measuring thyroid hormones or indirectly, by assessing TSH concentrations, which inversely reflects the thyroid hormone concentration sensed by the pituitary[24]. Therefore, serum TSH measurements might offer a better sensitivity for detecting thyroid dysfunction in comparison to fT3 and fT4 testing. This is especially important in light of our results regarding the positive association between TSH and ADHD diagnosis in children.

Solid evidence points to thyroid function being pivotal for brain development[38–41]. As this holds true for all stages of brain development, maternal thyroid function is important for early brain development while childhood thyroid function is important for subsequent stages of the maturing brain[42,43]. Our analysis showed that although the prevalence of ADHD diagnosis remains approximately the same between children and adolescents, thyroid hormones are different. In children with an ADHD diagnosis, serum TSH and fT4 were lower. In adolescents with either an ADHD diagnosis or ADHD symptoms, fT3 was higher. Hence, serum TSH and fT3 may influence the risk for ADHD.

In our cohort, a 1 mIU/L higher TSH was related to a 10% lower risk for ADHD in children previously diagnosed with ADHD. These data may support the importance of TSH during early brain development, since these associations disappeared in adolescents. In addition, since we found no significant relations between TSH and fT4 with ADHD symptoms, our results suggest that these parameters may not be suitable for ADHD diagnosis in adolescents. In addition, it should be noted that the positive association of fT3 with ADHD symptoms might simply be measures of behavior at the high-end normal variation for the *Inattention/Hyperactivity* scale.

While earlier investigations explored the association between severe thyroid dysfunction and ADHD in children and adolescents, these cases, 224 in total, were excluded from our analysis. Thyroid function and ADHD

	Children (tanner stage I–III)				Adolescents (tanner stage IV–V)			
	ADHD symptoms	Control	Total	*p*	ADHD symptoms	Control	Total	*p*
n	486	7754	8240		73	2667	2740	
TSH, mIU/L	2.4 (1.8; 3.1)	2.3 (1.7; 3.0)	2.3 (1.7; 3.0)	0.07	1.7 (1.2; 2.3)	1.8 (1.3; 2.5)	1.8 (1.3; 2.5)	0.40
fT3, pmol/L	6.2 (5.7; 6.8)	6.2 (5.7; 6.7)	6.2 (5.7; 6.7)	0.66	6.0 (5.3; 6.7)	5.7 (5.1; 6.3)	5.7 (5.1; 6.3)	0.006
fT4, pmol/L	18.1 (16.7; 19.8)	18.2 (16.8; 19.8)	18.2 (16.8; 19.8)	0.38	17.8 (16.4; 19.6)	18.1 (16.5; 19.9)	18.1 (16.5; 19.9)	0.37
Low TSH[a], n (%)	7 (1.44)	139 (1.79)	146 (1.77)		0 (0)	17 (0.64)	17 (0.62)	
High TSH[a], n (%)	16 (3.29)	226 (2.91)	242 (2.94)		5 (6.85)	127 (4.76)	132 (4.82)	
Low fT3 [a], n (%)	16 (3.29)	341 (4.40)	357 (4.33)		1 (1.37)	86 (3.22)	87 (3.18)	
High fT3[a], n (%)	8 (1.65)	148 (1.91)	156 (1.89)		3 (4.11)	61 (2.29)	64 (2.34)	
Low fT4[a], n (%)	3 (0.62)	58 (0.75)	61 (0.74)		0 (0%)	8 (0.30)	8 (0.29)	
High fT4[a], n (%)	47 (9.67)	828 (10.68)	875 (10.62)		6 (8.22)	215 (8.06)	221 (8.07)	
Males, n (%)	296 (60.91)	3821 (49.28)	4117 (49.96)		44 (60.27)	1222 (45.82)	1266 (46.20)	
Age, years	8.2 (5.6; 10.6)	8.9 (6.2; 11.6)	8.8 (6.1; 11.5)	< 0.001	15.0 (14.3; 16.4)	15.6 (14.4; 16.8)	15.6 (14.4; 16.7)	0.04
BMI, kg/m^2	16.4 (15.1; 18.2)	16.7 (15.3; 19.0)	16.6 (15.3; 19.0)	0.007	21.0 (19.2; 23.1)	21.0 (19.3; 23.4)	21.0 (19.3; 23.4)	0.80
Weight at birth, g	3350 (3000; 3650)	3420 (3090; 3750)	3410 (3080; 3750)	0.003	3370 (3020; 3800)	3380 (3070; 3700)	3380 (3070; 3700)	0.92
Maternal characteristics								
Gestational week at birth	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.03	40 (38; 40)	40 (39; 40)	40 (39; 40)	0.36
Gestational smoking, n (%)	143 (29.9)	1175 (15.3)	1318 (16.19)		21 (30.43)	419 (15.94)	440 (16.31)	
Socioeconomic status	10 (7; 12)	11 (9; 15)	11 (9; 15)	< 0.001	11 (8; 13)	11 (9;15)	11 (9;15)	0.09

Table 2. Characteristics of the study population by ADHD symptoms cases. Continuous data expressed as median and 25th/75th percentiles; nominal data expressed as total numbers and percentages; significance levels for continuous data was determined with the test for difference in median. *TSH* thyroid stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxine, *BMI* body mass index. [a]Defined according to Kratzsch et al[36].

	ADHD diagnosis		ADHD symptoms	
	Categorical		Categorical	
	Children (tanner I–III)	Adolescents (tanner IV–V)	Children (tanner I–III)	Adolescents (tanner IV–V)
	OR (CI)	OR (CI)	OR (CI)	OR (CI)
TSH, mIU/L	0.90 (0.81; 1.00)*	1.05 (0.90; 1.23)	1.00 (1.00; 1.01)	1.00 (0.78; 1.28)
fT3, pmol/L	1.00 (0.88; 1.12)	1.03 (0.81; 1.30)	1.02 (0.92; 1.14)	1.16 (0.89; 1.51)
fT4, pmol/L	0.96 (0.91; 1.01)	0.94 (0.86; 1.03)	0.97 (0.92; 1.02)	0.99 (0.90; 1.09)

Table 3. Results for the linear regression analysis between thyroid function biomarkers and ADHD diagnosis and ADHD symptoms. Presented are adjusted odds ratios (OR) with 95% Confidence Interval (CI). Models have been adjusted for sex, age, and weight at birth, and the following covariates: mother's smoking habit during gestation and the current BMI z-score of the child/adolescent. *TSH* thyroid stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxine. *$p \leq 0.05$.

symptoms may have changed significantly since the medication was initiated; therefore, it is difficult to assess the influence of present thyroid function when participants are on thyroid medication.

This investigation has several limitations. First, ADHD diagnosis was parent-reported after a previous diagnosis by a physician or psychologist and the age of the children/adolescents at time of diagnosis is unknown. We do acknowledge that when assessing ADHD symptoms, multi-informant rating scales are highly recommended and widely used to assist in decision-making[2,44]. Unfortunately, collecting additional information from teachers and/or relatives was unfeasible in this cohort study with more than 10,000 participants. Second, the use of stimulant medication (e.g. methylphenidate) in participants with an ADHD diagnosis was not assessed in the

	ADHD symptoms	
	Continuous	
	Children (tanner I–III)	Adolescents (tanner IV–V)
	β (CI)	β (CI)
TSH, mIU/L	0.00 (−0.03; 0.04)	0.03 (−0.10; 0.04)
fT3, pmol/L	0.08 (0.03; 0.14)*	0.07 (−0.02; 0.16)
fT4, pmol/L	−0.02 (−0.04; 0.00)	−0.02 (−0.06; 0.01)

Table 4. Results for the linear regression analysis between thyroid function biomarkers and ADHD symptoms continuously assessed by the *inattention/hyperactivity* subscale. Presented are beta-coefficients and 95% confidence intervals (CI) for a one unit change in thyroid function biomarker. Models have been adjusted for sex, age, and weight at birth, and the following covariates: mother's smoking habit during gestation and the current BMI z-score of the child/adolescent. *TSH* thyroid stimulating hormone, *fT3* free triiodothyronine, *fT4* free thyroxine. *$p \leq 0.05$.

questionnaire. However, methylphenidate treatment had no sustained effects on thyroid function in pre-pubertal children with ADHD[45]. Third, although both hypo- and hyperthyroidism in mothers during pregnancy have been associated with a greater risk of ADHD in children, the cohort did not include information on thyroid status of the mother during pregnancy. Fourth, our significant findings may be driven by our large sample size (more than 10,000 children and adolescents) influencing our p-values. Fifth, a meta-analysis of studies with longitudinal follow-up of children with ADHD suggests that 35% of children recover whereas 50% meet criteria for ADHD in partial remission and 15% continue to meet full diagnostic criteria for ADHD[5,46]. Lastly, our cross-sectional study design cannot provide causal relationships between thyroid function biomarkers and ADHD diagnosis, therefore a longitudinal analysis should assess when and how thyroid dysfunction may contribute to the pathophysiology of ADHD.

Nonetheless, this analysis also has several strengths. Our study population consisted of a very large cohort of children and adolescents (n > 10,000) representative of the German youth. Specifically, the information on numerous potential confounders was available. For the assessment of ADHD symptoms of participants aged 3 to 11 years, a behavioral assessment was conducted during medical examination in addition to the Strengths and Difficulties Questionnaire (SDQ) score of the parents' questionnaire. Moreover, a central laboratory was used to measure age-specific TSH, fT3, fT4 thereby reducing variability.

The various short- and long-term medical, social and health economic consequences of ADHD illustrate the high level of public health relevance of this disorder. Yet, possibilities of primary prevention are limited due to the high proportion of genetic factors in the etiology of ADHD. The association of thyroid dysfunction with neurodevelopmental disorders has always been of special interest because the brain is a target organ for thyroid hormones, and even small differences in neurobehavioral outcomes can have major public health consequences[47]. The association between TSH and ADHD diagnosis in children within the KiGGS Baseline study further highlights the significance to promote investigations to explore this interaction. Also, the lack of an association between TSH and ADHD diagnosis in adolescents points to important timing considerations for treatment options.

Methods

Participants and study design. KiGGS Baseline is based on a cross-sectional, nationally representative sample of children and adolescents 0–17 years of age with their main residence in Germany[48]. The sampling procedure followed a two-stage protocol developed in cooperation with the Centre for Survey Research and Methodology (ZUMA), Mannheim, Germany. First, to consider proportionately the population size according to degree of urbanization and geographic distribution in Germany, 167 communities were selected as primary sample units (PSUs), with a disproportionate number of PSUs in Berlin and East as well as West Germany, to represent these regions separately. At the second stage, an equal number of addresses (n = 24) per birth cohort was randomly selected (simple random sample) from local population registries within selected PSUs, eight weeks before the start of examinations. A final simple random sample was drawn at the Robert Koch Institute (RKI, Berlin, Germany), including a total of eight, nine, or ten children and adolescents per birth cohort, depending on community size. The total KiGGS Baseline sample included 28,299 children and adolescents. The ethics committee of the Charité/University Medicine Berlin approved the study.

Parents of eligible children and adolescents were contacted by letter and invited to participate in the survey. Following a random route plan, 167 PSUs were covered by four study teams within three years (May 19, 2003 to May 6, 2006). Personal contact was sought to those who had not responded to the invitation letter. A total of 17,641 children and adolescents participated in the study (response 66.6%). The parents of all participants gave informed written consent.

For the purpose of our study of the 17,641 KiGGS Baseline participants, children younger than three years were excluded (n = 2805) because of inadequate blood sample volume to measure thyroid function biomarkers. Further, we excluded 224 participants taking thyroid medication and 2871 participants with missing data for serum TSH levels or other co-variables leaving 11,588 participants for the analysis of thyroid function biomarkers and ADHD diagnosis. For the second regression analysis, assessing the relation between thyroid function

biomarkers and ADHD symptoms, missing data was present for 36 participants. Further, the 572 ADHD diagnosed individuals were excluded in this analysis resulting in a final sample size of 10,980 children and adolescents.

Interview and physical examination. The examination and interview component, which was tailored to age range, was carried out in a Standard Operating Procedure (SOP)-compliant, standardized manner. Each team involved in the study, which consisted of a physician and two examiners, attended a comprehensive training program explaining the guidelines set out in the SOP manuals before starting fieldwork. Follow-up training was regularly carried out during the data collection phase as required. Children's age, sex, birth weight, gestational week at birth as well as maternal smoking during gestation (regularly, occasionally, never) and family's socioeconomic status (SES), which was defined as "low", "medium", or "high" based on an established and validated index by Winkler and Stolzenberg[49], were determined using computer-assisted parental interviews conducted by a study physician. This multidimensional aggregated SES index comprises the dimensions of parents' education (school education and professional qualifications), income (net household income of all household members), and occupational status. In addition, a broad range of health information was collected from a self-administered questionnaire. These questionnaires were child age group-specific and administered to parents of all participants aged 0–17 years and in addition directly to participants aged 11–17 years. The parental questionnaire included a question on whether their child had been diagnosed with ADHD according to the established symptom profile (10th edition; ICD-10[50]) through a multi-informant assessment[2]. From the already frequently tested and validated Strengths and Difficulties Questionnaire (SDQ)[51] the subscale *Inattention /Hyperactivity* was included in the parental questionnaire. To determine ADHD symptoms the cutoff value of the English standard random sample was used[52], which is identical with the cut-off value of the German standardization[53]. The internal consistency of Subscale *Inattention/Hyperactivity* is $\alpha = 0.59$ and varies from 0.52 (lowest value, age group 3–6 years) to 0.63 (highest value, age group 11–13 years)[54]. Although a multi-informant assessment was not feasible to be ascertained in the KiGGS study setting, an additional behavioral assessment was carried out independently from the parental *Inattention/Hyperactivity* assessment by the study team during the physical examination ($n = 7,919$) for the age group of 3- to 11-year-olds. The criteria for the behavioral assessment conducted by the study team were oriented on the three main symptoms of ADHD: inattention, restlessness, impulsivity. Resulting from the parental questionnaires, participants were categorized as ADHD diagnosis cases, if a doctor or psychologists had diagnosed ADHD previously. ADHD symptoms were determined as followed: participants age 3- to 11-years-old, who scored a sum value of ≥ 7 in the *Inattention/Hyperactivity* scale of the SDQ and in addition received a positive behavioral assessment from the study team, yet had no previous ADHD diagnosis, were assigned in this group. For participants older than 11 years, the SDQ subscale result determined the ADHD symptoms. Participants were assigned to the control group for our first round of analyses, if no previous ADHD diagnosis was attested. In our second round of analyses, the control group consisted of participants with no previous ADHD diagnosis and whose behavioral assessment and the SDQ subscale result pointed towards no ADHD symptoms.

Participant BMI was calculated by dividing body weight in kg by height in cm to the square, which was measured during the physical examination. The Tanner Scale was observed by the study examiner and used to describe physical development[55]. The Tanner stages one through five were assigned based on the participants' external primary and secondary sex characteristics, such as breast size and development of pubic hair. Afterwards all participants were classified into two groups according to their Tanner status: children (stages one through three) and adolescents (stages four and five). The differentiation by physical development was chosen as there are substantial changes in TSH and thyroid hormone levels during childhood, in particular for fT3, which appear to relate to pubertal readiness[56].

Thyroid function biomarkers. A non-fasting blood sample was drawn during the appointment for the health interview and examination and processed within 45 minutes[57]. TSH, fT3, and fT4 were determined using electrochemiluminescence (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). The inter-serial coefficients of variation (CVs) were 3.9% for TSH, 5.9% for fT3, and 5.3% for fT4. The difference in the median serum TSH level was marginal regardless of the timing of the sample (morning, 2.11 mU/L; afternoon, 2.12 mU/L; evening, 2.31 mU/L) and unlikely to influence the results. As all measurements were conducted in the same laboratory, higher or lower thyroid hormone levels were defined using age- and sex-specific reference ranges[36].

Statistics. The total study population was stratified by Tanner status (children and adolescents) and the presence of an ADHD diagnosis or ADHD symptoms, which resulted in four different groups. Continuous data were expressed as median and 25th/75th percentiles (Q1 and Q3, respectively). Nominal data are provided as total numbers and percentages. Differences between groups were calculated using Kruskal–Wallis (continuous variables) and X^2 test (nominal variables), respectively. Associations of TSH, fT3 and fT4 with ADHD diagnosis as well as categorical ADHD symptoms were calculated using logistic regression models adjusted for sex, age, weight at birth, mother's smoking habit during pregnancy and current BMI z-score of the child/adolescent. Linear regression models adjusted for the same confounders were used to analyze the association between TSH, fT3 and fT4 with continuous ADHD symptoms. To account for potential non-linear relationships we modeled the exposure variable continuously and tested potential non-linear transformations of the exposure variable by sophisticated statistical methods such as fractional polynomials or restricted cubic splines to account for potential non-linear relationships of TSH/fT3/fT4 with ADHD diagnosis and symptoms. In our analyses, we found no evidence for non-linear associations. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed in Stata 14 (StataCorp. 2015. College Station, TX, USA).

Ethics approval and consent to participate. The parents/legal guardians of all participants gave informed written consent. The Ethics Committee of the Charité/University Medicine Berlin approved the study. Hence, all methods were carried out in accordance with relevant guidelines and regulations.

Data availability

The data that support the findings of this study are available from the Robert Koch Institute, Germany but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Robert Koch Institute.

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References

1. Getahun, D. *et al.* Recent trends in childhood attention-deficit/hyperactivity disorder. *JAMA Pediatr.* **167**, 282–288 (2013).
2. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Publishing, Philadelphia, 2013).
3. Thomas, R., Sanders, S., Doust, J., Beller, E. & Glasziou, P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* **135**, e994–e1001 (2015).
4. Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J. & Rohde, L. A. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am. J. Psychiatry* **164**, 942–948 (2007).
5. Faraone, S. V., Biederman, J. & Mick, E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol. Med.* **36**, 159–165 (2006).
6. Gizer, I. R., Ficks, C. & Waldman, I. D. Candidate gene studies of ADHD: a meta-analytic review. *Hum. Genet.* **126**, 51–90 (2009).
7. Faraone, S. V. *et al.* Molecular genetics of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **57**, 1313–1323 (2005).
8. Nikolas, M. A. & Burt, S. A. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. *J. Abnorm. Psychol.* **119**, 1 (2010).
9. Thapar, A., Holmes, J., Poulton, K. & Harrington, R. Genetic basis of attention deficit and hyperactivity. *Br J Psychiatry* **174**, 105–111 (1999).
10. Thapar, A., Cooper, M., Eyre, O. & Langley, K. Practitioner review: what have we learnt about the causes of ADHD?. *J. Child Psychol. Psychiatry* **54**, 3–16 (2013).
11. Nigg, J. T., Lewis, K., Edinger, T. & Falk, M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *J. Am. Acad. Child Adolesc. Psychiatry* **51**, 86–97 (2012).
12. Gustavson, K. *et al.* Smoking in pregnancy and child ADHD. *Pediatrics* **139**, e20162509 (2017).
13. Huang, L. *et al.* Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. *Pediatrics* **141**, e20172465 (2018).
14. Andersen, S. L., Laurberg, P., Wu, C. & Olsen, J. Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study. *BJOG Int. J. Obstet. Gynaecol.* **121**, 1365–1374 (2014).
15. Andersen, S. L., Andersen, S., Vestergaard, P. & Olsen, J. Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: a Danish nationwide case-cohort study. *Thyroid* **28**, 537–546 (2018).
16. Ghassabian, A. *et al.* Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatr. Res.* **69**, 454 (2011).
17. Ghassabian, A. *et al.* Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. *Thyroid* **22**, 178–186 (2012).
18. Drover, S. S. *et al.* Maternal thyroid function during pregnancy or neonatal thyroid function and attention deficit hyperactivity disorder: a systematic review. *Epidemiology (Cambridge, Mass.)* **30**, 130 (2019).
19. Abel, M. H. *et al.* Maternal iodine intake and offspring attention-deficit/hyperactivity disorder: Results from a large prospective cohort study. *Nutrients* **9**, 1239 (2017).
20. Bauer, M., Goetz, T., Glenn, T. & Whybrow, P. The thyroid-brain interaction in thyroid disorders and mood disorders. *J. Neuroendocrinol.* **20**, 1101–1114 (2008).
21. Constant, E. *et al.* Cerebral blood flow and glucose metabolism in hypothyroidism: a positron emission tomography study. *J. Clin. Endocrinol. Metab.* **86**, 3864–3870 (2001).
22. Ahmed, O. M., El-Gareib, A., El-Bakry, A., Abd El-Tawab, S. & Ahmed, R. Thyroid hormones states and brain development interactions. *Int. J. Dev. Neurosci.* **26**, 147–209 (2008).
23. Zader, S. J., Williams, E. & Buryk, M. A. Mental health conditions and hyperthyroidism. *Pediatrics* **144**, e20182874 (2019).
24. Álvarez-Pedrerol, M. *et al.* TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. *Clin. Endocrinol.* **66**, 890–898 (2007).
25. Valentine, J. *et al.* Thyroid function in a population of children with attention deficit hyperactivity disorder. *J. Paediatr. Child Health* **33**, 117–120 (1997).
26. Weiss, R. E., Stein, M. A., Trommer, B. & Refetoff, S. Attention-deficit hyperactivity disorder and thyroid function. *J. Pediatr.* **123**, 539–545 (1993).
27. Spencer, T., Biederman, J., Wilens, T., Guite, J. & Harding, M. ADHD and thyroid abnormalities: a research note. *J. Child Psychol. Psychiatry* **36**, 879–885 (1995).
28. May, T., Adesina, I., McGillivray, J. & Rinehart, N. J. Sex differences in neurodevelopmental disorders. *Curr. Opin. Neurol.* **32**, 622–626 (2019).
29. Murray, A. L. *et al.* Sex differences in ADHD trajectories across childhood and adolescence. *Dev. Sci.* **22**, e12721 (2019).
30. Cortese, S. *et al.* Association between ADHD and obesity: a systematic review and meta-analysis. *Am. J. Psychiatry* **173**, 34–43 (2016).
31. Nigg, J. T. *et al.* Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: new data and meta-analysis. *Clin. Psychol. Rev.* **43**, 67–79 (2016).
32. Ask, H. *et al.* Association of gestational age at birth with symptoms of attention-deficit/hyperactivity disorder in children. *JAMA Pediatr.* **172**, 749–756 (2018).
33. Franz, A. P. *et al.* Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. *Pediatrics* **141**, e20171645 (2018).
34. Soneji, S. & Beltrán-Sánchez, H. Association of maternal cigarette smoking and smoking cessation with preterm birth. *JAMA Netw. Open* **2**, e192514–e192514 (2019).
35. Inoue, S. *et al.* Impact of maternal and paternal smoking on birth outcomes. *J. Public Health* **39**, 1–10 (2017).

36. Kratzsch, J. *et al.* Reference intervals for TSH and thyroid hormones are mainly affected by age, body mass index and number of blood leucocytes, but hardly by gender and thyroid autoantibodies during the first decades of life. *Clin. Biochem.* **41**, 1091–1098 (2008).
37. Villanger, G. D. *et al.* Neonatal thyroid-stimulating hormone and association with attention-deficit/hyperactivity disorder. *Paediatr. Perinat. Epidemiol.* **34**(5), 590-596 (2020).
38. Chevrier, J. *et al.* Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age. *J. Thyroid Res.* **2011**, 426427. https://doi.org/10.4061/2011/426427 (2011).
39. Haddow, J. E. *et al.* Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N. Engl. J. Med.* **341**, 549–555 (1999).
40. Vermiglio, F. *et al.* Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J. Clin. Endocrinol. Metab.* **89**, 6054–6060 (2004).
41. Päkkilä, F. *et al.* The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child. *J. Clin. Endocrinol. Metab.* **99**, E1–E8 (2014).
42. Bernal, J. Thyroid hormone receptors in brain development and function. *Nat. Rev. Endocrinol.* **3**, 249 (2007).
43. Rovet, J. F. *Paediatric Thyroidology* Vol. 26, 26–43 (Karger Publishers, Berlin, 2014).
44. De Los Reyes, A. *et al.* The validity of the multi-informant approach to assessing child and adolescent mental health. *Psychol. Bull.* **141**, 858 (2015).
45. Bereket, A. *et al.* Height, weight, IGF-I, IGFBP-3 and thyroid functions in prepubertal children with attention deficit hyperactivity disorder: effect of methylphenidate treatment. *Hormone Res. Paediatr.* **63**, 159–164 (2005).
46. Weiss, G., Hechtman, L., Milroy, T. & Perlman, T. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. *J. Am. Acad. Child Psychiatry* **24**, 211–220 (1985).
47. Bellanger, M., Demeneix, B., Grandjean, P., Zoeller, R. T. & Trasande, L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **100**, 1256–1266 (2015).
48. Kurth, B.-M. *et al.* The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. *BMC Public Health* **8**, 196 (2008).
49. Winkler, J. & Stolzenberg, H. D. Sozialschichtindex im Bundes-Gesundheitssurvey. *Gesundheitswesen* **61**, S178–S183 (1999).
50. Organization, W. H. *International Statistical Classification of Diseases and Related Health Problems: 10th Revision (ICD-10)*. https://www.who.int/classifications/apps/icd/icd (1992).
51. Goodman, R. Psychometric properties of the strengths and difficulties questionnaire. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 1337–1345 (2001).
52. Goodman, R., Ford, T., Simmons, H., Gatward, R. & Meltzer, H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *Int. Rev. Psychiatry* **15**, 166–172 (2003).
53. Woerner, W., Becker, A. & Rothenberger, A. Normative data and scale properties of the German parent SDQ. *Eur Child Adolesc. Psychiatry* **13**, ii3–ii10 (2004).
54. Hölling, H., Erhart, M., Ravens-Sieberer, U. & Schlack, R. Verhaltensauffälligkeiten bei Kindern und Jugendlichen. *Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz* **50**, 784–793 (2007).
55. Tanner, J. M. & Whitehouse, R. H. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch. Dis. Child.* **51**, 170–179 (1976).
56. Taylor, P. N. *et al.* Maturation in serum thyroid function parameters over childhood and puberty: results of a longitudinal study. *J. Clin. Endocrinol. Metab.* **102**, 2508–2515 (2017).
57. Thierfelder, W., Dortschy, R., Hintzpeter, B., Kahl, H. & Scheidt-Nave, C. Biochemical measures in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* **50**, 757–770 (2007).

Author contributions

D.A. as well as M.B. and T.I. analyzed and interpreted the data, drafted the manuscript and approved the final version of the manuscript. M.T. designed the data collection instruments, coordinated and supervised data collection, and reviewed and revised the manuscript. H.J.G. and H.V. critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Competing interests

The authors declare no competing interests.

Additional information

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Standardized Map of Iodine Status in Europe

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Background: Knowledge about the population's iodine status is important, because it allows adjustment of iodine supply and prevention of iodine deficiency. The validity and comparability of iodine-related population studies can be improved by standardization, which was one of the goals of the EUthyroid project. The aim of this study was to establish the first standardized map of iodine status in Europe by using standardized urinary iodine concentration (UIC) data.

Materials and Methods: We established a gold-standard laboratory in Helsinki measuring UIC by inductively coupled plasma mass spectrometry. A total of 40 studies from 23 European countries provided 75 urine samples covering the whole range of concentrations. Conversion formulas for UIC derived from the gold-standard

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values were established by linear regression models and were used to postharmonize the studies by standardizing the UIC data of the individual studies.

Results: In comparison with the EUthyroid gold-standard, mean UIC measurements were higher in 11 laboratories and lower in 10 laboratories. The mean differences ranged from −36.6% to 49.5%. Of the 40 postharmonized studies providing data for the standardization, 16 were conducted in schoolchildren, 13 in adults, and 11 in pregnant women. Median standardized UIC was <100 μg/L in 1 out of 16 (6.3%) studies in schoolchildren, while in adults 7 out of 13 (53.8%) studies had a median standardized UIC <100 μg/L. Seven out of 11 (63.6%) studies in pregnant women revealed a median UIC <150 μg/L.

Conclusions: We demonstrate that iodine deficiency is still present in Europe, using standardized data from a large number of studies. Adults and pregnant women, particularly, are at risk for iodine deficiency, which calls for action. For instance, a more uniform European legislation on iodine fortification is warranted to ensure that noniodized salt is replaced by iodized salt more often. In addition, further efforts should be put on harmonizing iodine-related studies and iodine measurements to improve the validity and comparability of results.

Keywords: iodine, iodine supply, epidemiology, method comparison

Introduction

THE IODINE STATUS of regions is assessed by median urinary iodine concentrations (UICs) determined in representative samples of populations. National iodine fortification programs are initiated and modified based on such studies. According to the World Health Organization (WHO), a region is iodine sufficient if the median UIC is ≥100 μg/L in nonpregnant populations (1). Based on this criterion, worldwide maps of country-specific iodine status are drawn (2,3). Laboratory methods for measuring UIC, however, are heterogeneous, hampering the comparability of iodine monitoring studies (1). In a recent ring trial in Germany consisting of 300 samples, variations of up to 50% were observed between different UIC laboratory methods. These findings emphasize the need for standardization of iodine monitoring status as well as UIC measurements, ensuring valid estimates of the iodine status in populations (4).

Besides the standardization of iodine monitoring studies, it will be necessary to harmonize fortification programs. In Europe, iodine fortification programs differ according to type of regulations (mandatory vs. voluntary iodine fortification), amount of iodine used, and chemical form (iodine vs. iodate) (5,6). The variety of iodine fortification programs within Europe is a challenge for companies acting on the global market. In consequence, large parts of Europe can be seen as mildly to moderately iodine deficient with only 27% of European households having access to iodized salt (7). Around 350 million citizens are exposed to iodine deficiency being at higher risk for developing neurodevelopmental anomalies, since iodine deficiency remains as an important yet preventable cause of brain damage (7). In contrast, the ''Global Scorecard of Iodine Nutrition 2017'' provided by the Iodine Global Network (IGN) shows that large parts of Europe are adequately supplied by iodine (2). This discrepancy may be explained by a lack of standardization of iodine measurements used for the IGN scorecard. Furthermore, iodine status is reported at the national level in the IGN map, but, particularly in countries with voluntary iodine supply, median iodine levels may differ substantially between subpopulations and regions within the respective country. Therefore, harmonized monitoring studies and UIC measurements as well as the consideration of regional and population differences are of great importance when evaluating and monitoring the effectiveness of fortification programs. In our study, we aimed to standardize European iodine monitoring studies with respect to these considerations to establish a valid map of the iodine status in European populations.

Materials and Methods

Within the framework of the EUthyroid consortium, we collected data on iodine status from 48 European studies using the EUthyroid data exchange system (8). Information on data owner, study design (population based, volunteers, or patients), study population (children, adults, or pregnant women), year of data collection, blood sampling, urine collection, and laboratory methods was collected from each study. Details of the included studies can be found in Supplementary Table S1. The maximum number of studies, for which UICs were analyzed in one laboratory, was three. The study region was assessed using the EU-recommended ''Nomenclature of Territorial Units for Statistics'' system, which classifies each European country by five hierarchical levels (9). For each study participating in the cross-laboratory comparison, the relevant ethics approval was obtained and each study followed the declaration of Helsinki.

The individual studies were postharmonized by standardizing the UIC data. For this purpose, we established a gold-standard EUthyroid laboratory at Finnish Institue for Health and Welfare in Helsinki, where UIC was measured with inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7800 ICP-MS system (Agilent Technologies, Inc., Santa Clara, CA). One-hundred microliters of urine was extracted using ammonium hydroxide solution. Iodine was scanned on m/z = 127 and tellurium was used as internal standard. The National Institute of Standards and Technology reference standard materials SRM2670a (with certified mass concentration value) and SRM3668 Level 1 and Level 2 were used to ensure accuracy of urinary iodine determinations. Coefficient of variation of control samples was 2.9% ± 0.8% during the course of the study. The laboratory participates regularly successfully in the external quality assessment scheme ''Ensuring the Quality of Urinary Iodine Procedures'' organized by the Centers for Disease Control and Prevention.

For standardization of the UIC data from the individual studies, each partner was asked to send 75 spot urine samples to the EUthyroid gold standard laboratory. This number was

a priori determined by a power analysis, accounting for the variation of UIC measurements. Since the distribution of UICs varies according to current iodine supply of the respective study region, it is not useful to determine one strict cutoff to define these marginal areas. Instead the cutoffs should be determined study-specific based on distributional characteristics. To detect deviations at either end of the UIC distribution, the low and the high ends were oversampled. Thus, samples were selected the following way:

- Between 0 and 5th percentile—12 samples
- Between 5th percentile and 25th percentile—13 samples
- Between 25th percentile and 50th percentile—13 samples
- Between 50th percentile and 75th percentile—13 samples
- Between 75th percentile and 95th percentile—13 samples
- Between 95th percentile and 100th percentile—11 samples

Based on the comparisons, we calculated mean deviations ±1.96 standard deviations in percentage by Bland & Altman plots. Correlations between two laboratory methods were assessed by linear regression (10). Conversion formulas derived from linear regression models were established and applied to the original studies. We also recalculated formulas using Passing–Bablok regression for all laboratories and found no substantial differences to our findings when applying these formulas to the study data (data not shown).

Out of the 48 studies, 8 studies were not able to submit samples to the EUthyroid laboratory, resulting in a total number of 40 standardized studies from 23 European countries. Standardized UICs were calculated as median for each of the studies and plotted on the European map. Data analyses were conducted using Stata 15.1 (Stata Corporation, College Station, TX). Maps were generated in ArcGIS (Environmental Systems Research Institute (ESRI), ArcGIS Release 10.3.1, Redlands, CA).

Results

In comparison with the gold-standard EUthyroid laboratory, UIC measurements were on average higher in 11 laboratories and lower in 10 laboratories (Table 1). The mean differences ranged from −36.6% to 49.5%. Correlations of UICs to the gold-standard EUthyroid laboratory were ≥0.9 for 9 laboratories (42.9%), 0.8–0.9 for 5 laboratories (23.8%), 0.7–0.8 for 3 laboratories (14.3%), and <0.7 for 4 laboratories (19.0%). Conversion formulas used for generating standardized UIC values are given in Table 1.

Of the 40 standardized studies from 23 countries, 16 (40.0%) were conducted in schoolchildren, 13 (32.5%) in adults, and 11 (27.5%) in pregnant women. Table 2 gives the median standardized UIC for all 40 studies, and in Figure 1 the median standardized UICs are printed on the European map. Studies are presented depending on the exact study region (status is not extrapolated to the national level) and very small study regions are highlighted by circles for better visibility. In population monitoring of iodine status using UICs, schoolchildren have been least impacted by thyroid medication (11), therefore, preference has been given to studies carried out in schoolchildren. Thus, the UIC data have been selected for each country in the following order of

Table 1. Laboratory Comparisons with the EUthyroid Central Laboratory for Urinary Iodine Concentrations

Laboratory	*Difference in UICs; % Mean (1.96*SD)*	*Correlation*	p_{int}	p_{slope}	*Conversion formula*
1	−0.1 (14.7)	0.99	0.925	0.356	−0.23 + 1.01*UIC
2	−18.2 (53.2)	0.98	0.667	<0.001	−0.90 + 1.16*UIC
3	−15.5 (75.8)	0.98	0.022	0.458	17.44 + 0.98*UIC
4	13.0 (27.0)	0.97	<0.001	0.040	−29.2 + 1.04*UIC
5	−2.6 (49.7)	0.95	0.836	0.225	−1.05 + 1.04*UIC
6	32.3 (32.9)	0.95	0.074	<0.001	15.71 + 0.66*UIC
7	3.4 (37.2)	0.95	0.892	0.179	0.91 + 0.97*UIC
8	5.5 (79.2)	0.93	0.287	0.972	−5.65 + 1.00*UIC
9	14.5 (27.3)	0.92	0.693	<0.001	2.39 + 0.86*UIC
10	12.4 (44.4)	0.89	0.363	<0.001	5.02 + 0.83*UIC
11	−15.9 (143.9)	0.87	0.337	0.124	9.48 + 0.93*UIC
12	34.7 (89.9)	0.83	<0.001	<0.001	−67.37 + 1.54*UIC
13	49.5 (63.1)	0.82	0.163	<0.001	−6.61 + 0.63*UIC
14	30.0 (51.1)	0.82	0.096	0.161	−27.27 + 0.93*UIC
15	10.9 (83.2)	0.77	0.824	0.723	−6.39 + 0.98*UIC
16	−25.4 (74.3)	0.76	0.017	0.938	−89.08 + 1.92*UIC
17	−36.4 (62.0)	0.76	0.952	<0.001	−0.91 + 1.51*UIC
18	−18.4 (101.9)	0.68	<0.001	<0.001	68.21 + 0.63*UIC
19	4.4 (83.7)	0.62	0.042	0.009	20.94 + 0.80*UIC
20	−36.6 (131.8)	0.57	<0.001	<0.001	80.08 + 0.59*UIC
21	−16.5 (139.7)	0.50	<0.001	<0.001	49.23 + 0.53*UIC

Mean and SDs derived from Bland & Altman plots; correlations and conversion formulas from linear regression models; p_{int} and p_{slope} are the *p*-values derived from the regression model for the intercept = 0 and the slope = 1. $p < 0.05$ indicates significant difference.

SDs, standard deviations; UIC, urinary iodine concentration.

Table 2. Standardized Median Urinary Iodine Concentrations in European Monitoring Studies

Country	*Year*	*No. of individuals*	*Standardized median UIC in μg/L (95% CI)*	*Standardized interquartile range of UIC*
Studies in schoolchildren				
Croatia	2016	200	222 (209–235)	179–282
Czech Republic	2006	302	210 (194–225)	103–294
Germany	2006	14,641	113 (111–115)	61–169
Hungary	2018	110	254 (231–276)	163–337
Northern Ireland and Republic of Ireland	2015	901	110 (104–116)	71–162
Italy	2016	100	134 (126–143)	114–162
Latvia	2011	915	102 (93–111)	34–194
North Macedonia	2016	1167	216 (208–224)	149–291
Montenegro	2016	406	181 (168–193)	124–248
Norway	2015	457	98 (93–103)	69–135
Poland	2017	1000	121 (116–126)	82–168
Portugal	2011	4390	107 (106–108)	94–156
Serbia	2018	74	187 (170–204)	132–239
Spain	2011	1750	179 (174–184)	121–246
Sweden	2007	866	127 (122–132)	95–166
Switzerland	2016	727	152 (146–158)	115–201
Studies in adults				
Croatia	2016	227	178 (163—193)	111–222
Cyprus	2014	121	99 (87–111)	71–150
Czech Republic	2006	288	105 (101–108)	83–191
Finland	2017	1542	96 (93–100)	62–146
Germany	2012	4287	65 (63–66)	36–103
	2011	7022	51 (49–52)	26–82
	2008	2999	93 (90–96)	58–136
	2001	4260	72 (70–73)	41–107
Slovenia	2017	292	73 (63–83)	38–151
Spain	2010	4383	121 (118–124)	79–179
Sweden	2001	565	132 (123–140)	71–204
Switzerland	2016	345	103 (87–120)	63–184
Turkey	2017	165	116 (110–121)	89–145
Studies in pregnant women				
Croatia	2016	202	157 (147–167)	114–196
Greece	2015	1135	118 (114–123)	79–180
Hungary	2016	190	144 (126–161)	89–276
Latvia	2013	743	39 (35–44)	16–75
North Macedonia	2017	593	177 (161–192)	90–265
Poland	2017	300	113 (101–126)	64–188
Portugal	2011	4107	104 (103–105)	65–155
Romania	2016	317	159 (142–177)	99–243
Sweden	2007	459	114 (105–123)	73–162
Switzerland	2016	358	156 (135–177)	81–325
Northern Ireland (United Kingdom)	2015	240	66 (54–79)	32–113

CI calculated by bootstrapping with 500 repetitions.
CI, confidence interval.

priority: data from the most recent nationally representative survey carried out in (i) schoolchildren, (ii) adults, and (iii) pregnant women. In the absence of recent national surveys, subnational data were used in the same order of priority.

European maps of standardized UICs in schoolchildren, adults, and pregnant women are displayed in Figures 2–4 at the country level. Median standardized UIC was <100 μg/L in 1 out 16 (6.3%) studies in schoolchildren, while in adults 7 out of 13 (53.8%) studies had a median standardized UIC <100 μg/L. In tendency, countries from eastern Europe were better supplied by iodine than northern and western European countries. Seven out of 11 (63.6%) studies in pregnant women revealed a median standardized UIC <150 μg/L. In some countries, median UIC differed strongly across subpopulations. Especially in Latvia, but also in Germany, Switzerland, Spain, Czech Republic, and Macedonia, schoolchildren had higher median UICs than adults.

Discussion

We observed substantial differences in UIC measurements between different laboratories. These results show that standardizing UIC measurements is important when comparing results. Looking for example at the population-based

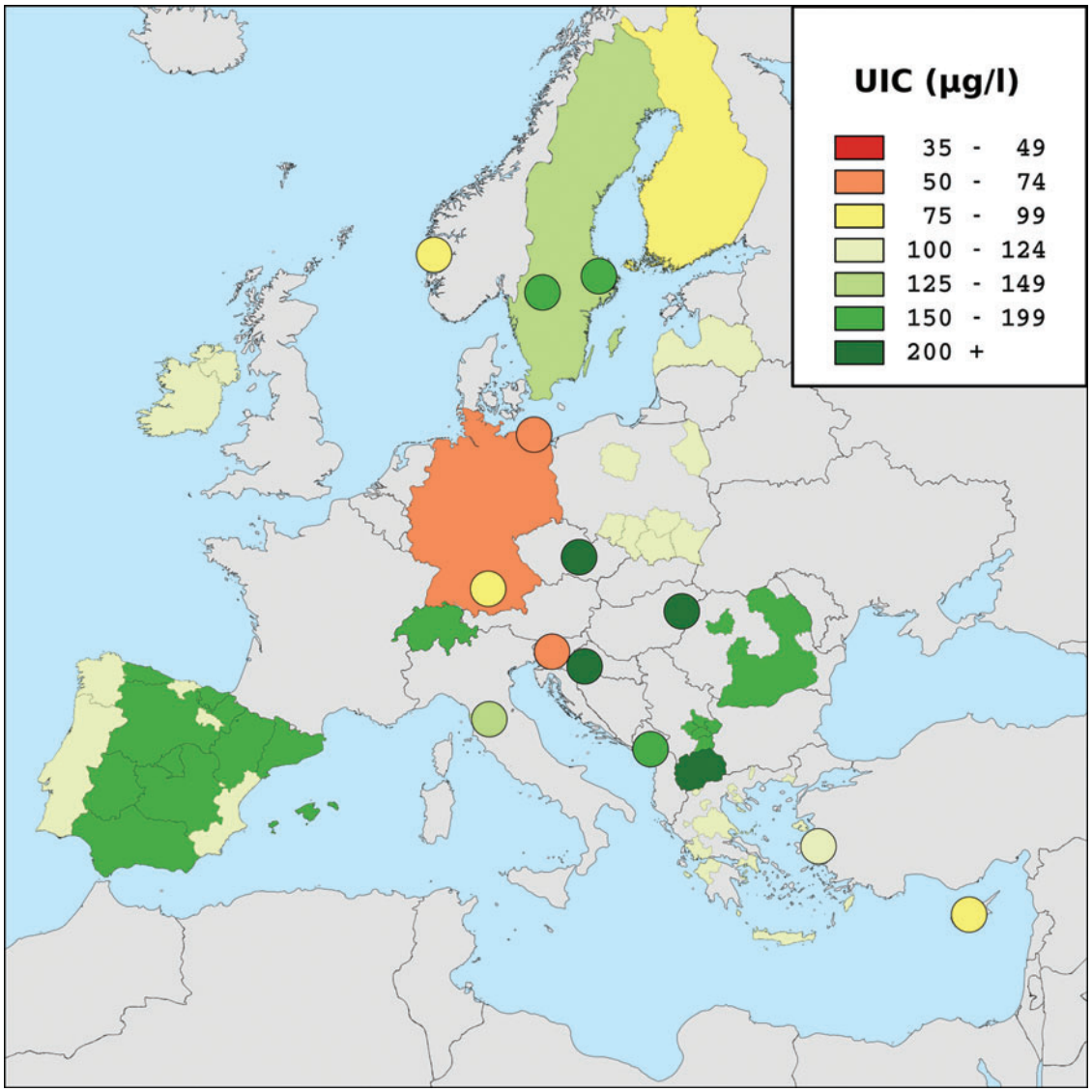

FIG. 1. Standardized European map of median UICs; studies have been selected for each country in the following order of priority: most recent study in (i) schoolchildren, (ii) adults, (iii) pregnant women; gray shadings indicate ''no data available.'' UICs, urinary iodine concentrations. Color images are available online.

German adults studies DEGS (nationwide, 2011), SHIP-Trend (northeast Germany, 2012), and KORA (south Germany, 2008), the range of nonstandardized median UICs varied substantially and was between 44 and 158 μg/L. Even though voluntary iodine fortification in Germany can lead to regional differences in iodine status, such large differences were not expected and do not seem plausible. However, different laboratories were responsible for the UIC measurements in the latter studies and we previously demonstrated larger differences in UIC measurements across these laboratories (4). While UIC measurements by Sandell–Kolthoff reaction were quite comparable with UIC measurements by the gold-standard ICP-MS for one laboratory, there were substantial differences in UICs for the other two laboratories using the Sandell–Kolthoff reaction compared with the ICP-MS method (4). Thus, we believe that a potential explanation for the differences across the laboratories is the use of different digestion methods (4). Particularly, an insufficient amount of the oxidizing digestion acid may result in elevated UIC measurements. After standardizing data from the European studies using the gold-standard EUthyroid laboratory, the median UICs were less variable, ranging between 51 and 93 μg/L, which indicates that Germany is currently mild to moderately iodine deficient.

Our standardized UIC data show that mild-to-moderate iodine deficiency is still common in the adult population and in pregnant women in Europe, according to WHO criteria (1). Schoolchildren, in contrast, are mostly iodine sufficient, according to this study. Compared with children and adolescents, adults are likely to obtain less iodine from the diet because of lower consumption of milk products, the main source of dietary iodine in many countries (12–14). This, together with larger urine volumes in adults compared with schoolchildren (15) or amount of liquids consumed, may explain the higher frequency of adult studies with median UIC <100 μg/L compared with studies in schoolchildren.

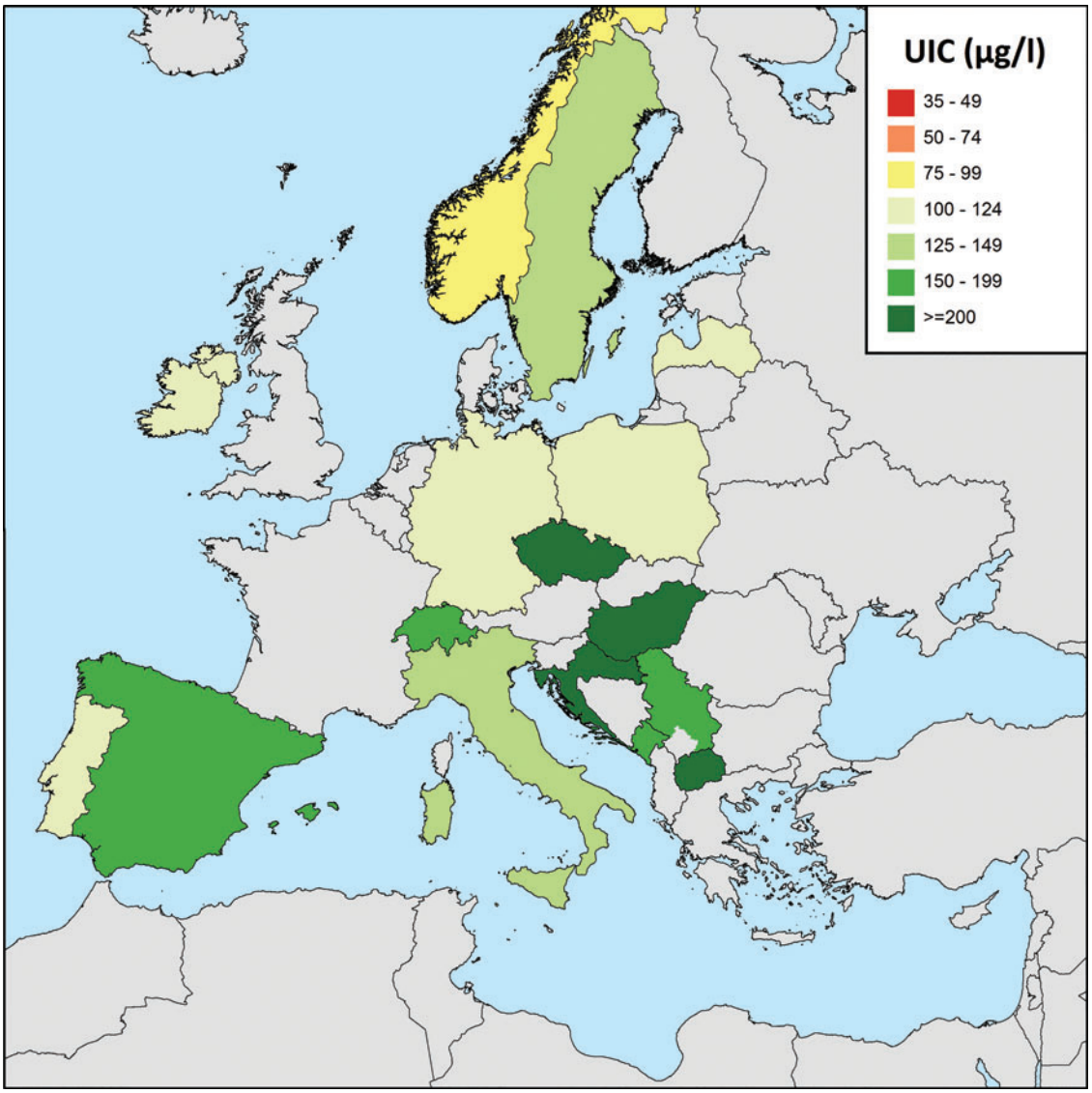

FIG. 2. Standardized European map of median UICs in schoolchildren; gray shadings indicate ''no data available.'' Color images are available online.

Pregnant women represent a specific subgroup of the general population. During pregnancy, iodine demand is higher and iodine clearance in the kidney increases, which is taken into account in the WHO pregnancy population cutoff for sufficient iodine supply (150 μg/L) in UIC (1). Pregnant women are recommended to take iodine supplementation in some countries (16), which hampers the comparison between iodine status in pregnant women and other populations in a study region. Furthermore, physiological changes during pregnancy and the fact that sample collection from pregnant women is sometimes performed in conjunction with ultrasound measurements, when they are advised to drink more water, lead to a higher dilution of the urine samples and in consequence to lower UICs (17). For these reasons, monitoring studies in pregnant women should not be used to characterize the iodine status of the general population and should be assessed separately from monitoring studies in children and adults. Our data demonstrate that pregnant women are particularly affected by iodine deficiency in Europe, emphasizing the importance of monitoring studies and an improved iodine status in this vulnerable subgroup.

Our standardized UIC data show iodine deficiency in 53.8% of all adult studies, but iodine deficiency in only 6.3% of studies in schoolchildren. The 2017 iodine scorecard of the IGN indicates only two European countries as iodine deficient, but in the IGN scorecard, the iodine status of all countries with data is based on studies in schoolchildren, with the exception of Finland (2). WHO recommends monitoring of UICs in school-age children as a proxy for the general population (1). Although WHO also defines adequate iodine intake in adults as a median UIC value $\geq$100 μg/L (1), the scientific basis for this threshold is weak (18). Future research to define a functional UIC cutoff value for adults indicating iodine deficiency would be valuable.

For the IGN scorecard, studies were not standardized, which may also be an explanation for the differences to our map. Another potential source of variation when comparing iodine surveys is the use of iodine–creatinine ratios (ICRs).

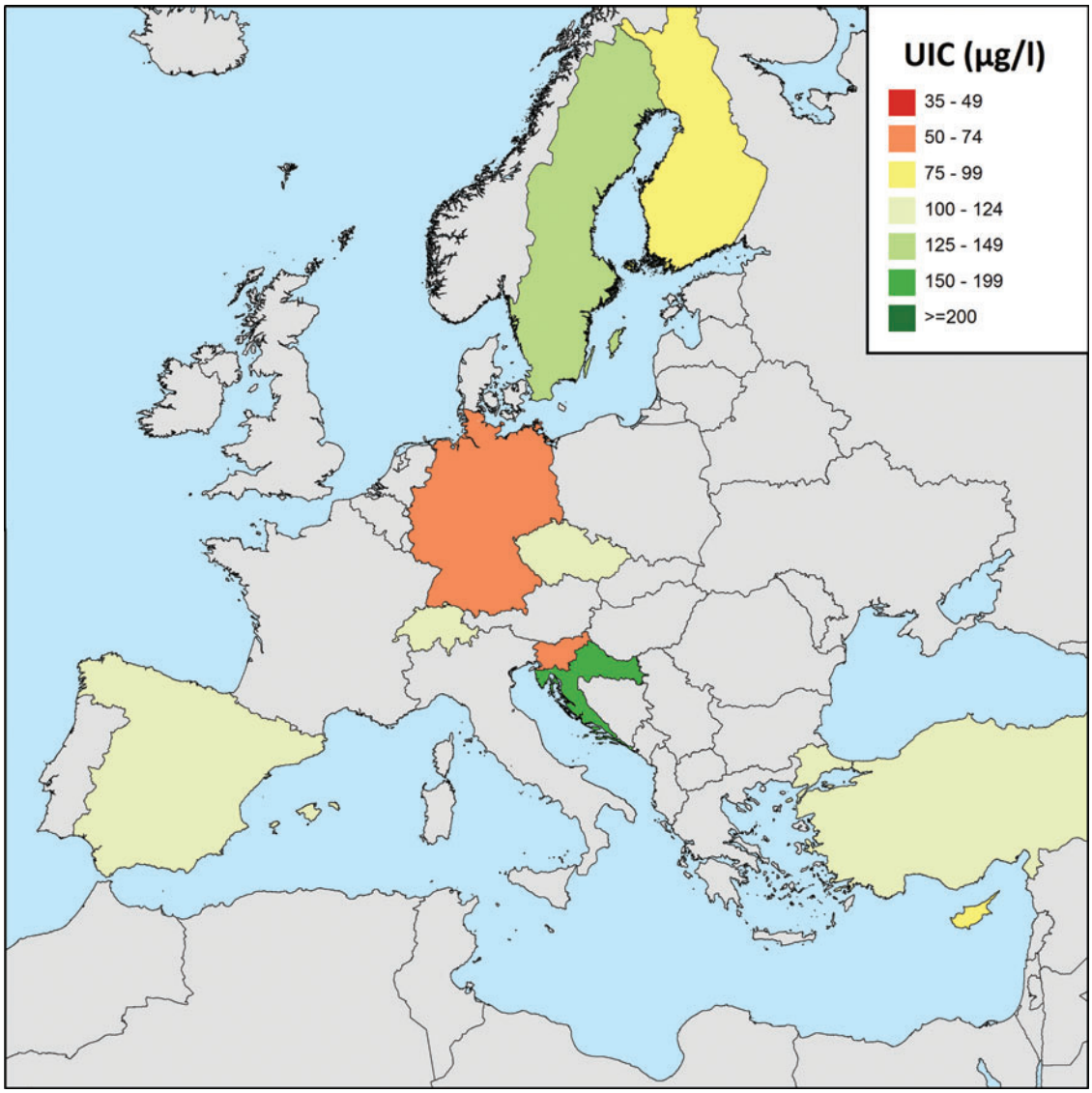

FIG. 3. Standardized European map of median UICs in adults; gray shadings indicate ''no data available.'' Color images are available online.

ICR has the advantage that UIC measurements are standardized to dilution of the urine samples, but the measurement error of ICR is larger than that for UIC, because two biomarkers are set into context. In large populations, the effect of the dilution of urine samples should cancel out. In a recent study, it was reported that a study size of 500 individuals is needed to determine the iodine level of a population with a precision of 5% (19). Thus, we recommend to analyze UICs instead of the ICR in larger population studies. In pregnant women, however, ICR data are useful, because of the large variation in the dilution of urine during pregnancy.

Iodine supply appears to be better in eastern European countries than in western or northern European countries. This may be due to the fact that in eastern Europe, iodine fortification programs are obligatory and well monitored, whereas in the rest of Europe, iodine fortification programs are mostly voluntary (6).

The major strength of our study is that we present, for the first time, standardized data on iodine status for Europe. For standardization of each laboratory, we used a sufficient number of samples ($n=75$) covering the whole range of UICs. The standardization approach was not ideal, because it was based on postharmonization of data from existing studies. However, it yields a general view of the current iodine status across Europe, and indicates that preharmonized studies are needed, as well as actions to improve iodine intake in certain population groups. The main limitations of our study arise from differences of the monitoring studies included, for example, in recruitment procedures (population based or not), size of study (ranging from 74 to 14,641 study participants), or timing of sample collection. Furthermore, subnational UIC surveys should be interpreted with caution. These surveys are commonly carried out to provide a rapid assessment of population iodine status, but due to a lack of sampling rigor, they may over- or underestimate the iodine status at the national level. Even though schoolchildren are the ideal population, they are not representative for adult populations, because adolescents and adults are expected to

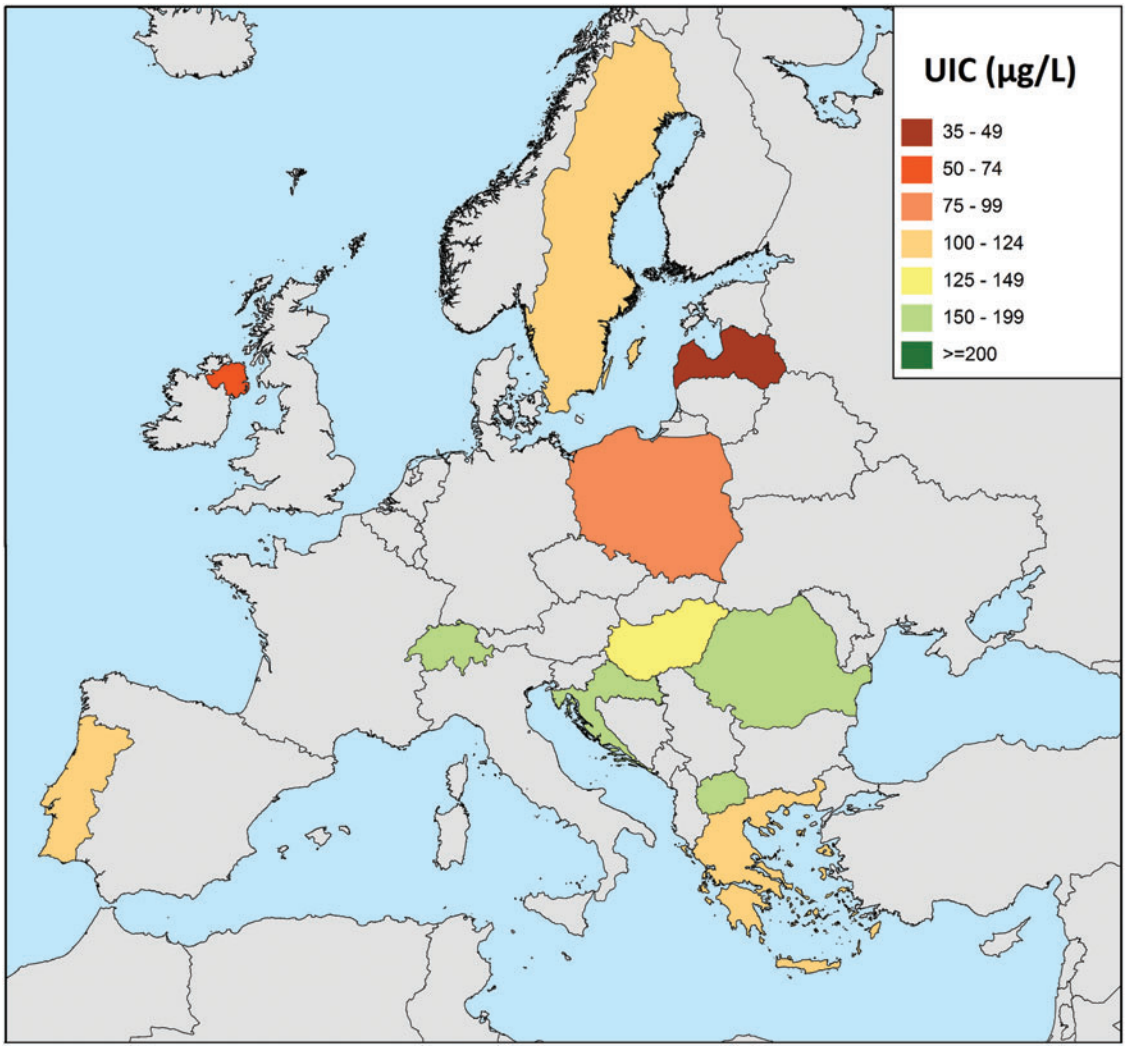

FIG. 4. Standardized European map of median UICs in pregnant women; gray shadings indicate ''no data available.'' Legend reflects adequate iodine intake in pregnant women with a median UIC of 150–249 μg/L as recommended by the World Health Organization (WHO). Color images are available online.

have a lower UICs due to differences in diet. Particularly, the consumption of milk varies significantly between these subpopulations.

In the EUthyroid project, we standardized the data from European iodine monitoring studies and demonstrated that iodine status is generally adequate in schoolchildren but iodine deficiency may still be present in adults and pregnant women. An improvement of the iodine supply in Europe is hampered by different national legislations, leading to a disproportionate use of iodized salt in processed food production (6). Therefore, a more uniform European legislation on iodine fortification is required. The standardized European map of UIC is an important milestone to provide robust evidence to encourage stakeholders to improve and harmonize legislations toward Europe and beyond. In future studies, much more effort should be put on harmonizing the procedures used in iodine monitoring studies, beginning from the planning phase and including sample collection procedures and UIC measurements, to improve the validity and comparability of iodine studies.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1

References

1. World Health Organization 2007 Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. A Guide for Programme Managers (Third edition). Available at https://apps.who.int/iris/bitstream/handle/10665/43781/9789241595827_eng.pdf (accessed July 9, 2020).
2. Iodine Global Network. Global map of iodine nutrition. Available at www.ign.org/scorecard.htm (accessed July 9, 2020).

3. Zimmermann MB, Andersson M 2012 Update on iodine status worldwide. Curr Opin Endocrinol Diabetes Obes **19:** 382–387.
4. Ittermann T, Johner S, Below H, Leiterer M, Thamm M, Remer T, Volzke H 2018 Interlaboratory variability of urinary iodine measurements. Clin Chem Lab Med **56:**441–447.
5. Nystrom HF, Brantsaeter AL, Erlund I, Gunnarsdottir I, Hulthen L, Laurberg P, Mattisson I, Rasmussen LB, Virtanen S, Meltzer HM 2016 Iodine status in the Nordic countries—past and present. Food Nutr Res **60:**31969.
6. Volzke H, Caron P, Dahl L, de Castro JJ, Erlund I, Gaberscek S, Gunnarsdottir I, Hubalewska-Dydejczyk A, Ittermann T, Ivanova L, Karanfilski B, Khattak RM, Kusic Z, Laurberg P, Lazarus JH, Markou KB, Moreno-Reyes R, Nagy EV, Peeters RP, Pirags V, Podoba J, Rayman MP, Rochau U, Siebert U, Smyth PP, Thuesen BH, Troen A, Vila L, Vitti P, Zamrazil V, Zimmermann MB 2016 Ensuring effective prevention of iodine deficiency disorders. Thyroid **26:**189–196.
7. Lazarus JH 2014 Iodine status in Europe in 2014. Eur Thyroid J **3:**3–6.
8. The EUthyroid Consortium. EUthyroid Data Exchange System Available at https://dex.euthyroid.medizin.uni-greifswald.de/dex/ (accessed December 9, 2018).
9. Eurostat. 2007 Regions in the European Union. Nomenclature of territorial units for statistics—NUTS 2006/EU-27. Office for Official Publications of the European Communities, Luxembourg.
10. Cashman KD, Dowling KG, Skrabakova Z, Kiely M, Lamberg-Allardt C, Durazo-Arvizu RA, Sempos CT, Koskinen S, Lundqvist A, Sundvall J, Linneberg A, Thuesen B, Husemoen LL, Meyer HE, Holvik K, Gronborg IM, Tetens I, Andersen R 2015 Standardizing serum 25-hydroxyvitamin D data from four Nordic population samples using the Vitamin D Standardization Program protocols: shedding new light on vitamin D status in Nordic individuals. Scand J Clin Lab Invest **75:**549–561.
11. Diaz A, Lipman Diaz EG 2014 Hypothyroidism. Pediatr Rev **35:**336–347; quiz 348–339.
12. Rasmussen LB, Ovesen L, Bulow I, Jorgensen T, Knudsen N, Laurberg P, Pertild H 2002 Dietary iodine intake and urinary iodine excretion in a Danish population: effect of geography, supplements and food choice. Br J Nutr **87:** 61–69.
13. Thamm M, Ellert U, Thierfelder W, Liesenkotter KP, Volzke H 2007 [Iodine intake in Germany. Results of iodine monitoring in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **50:**744–749.
14. Dahl L, Opsahl JA, Meltzer HM, Julshamn K 2003 Iodine concentration in Norwegian milk and dairy products. Br J Nutr **90:**679–685.
15. Johner SA, Shi L, Remer T 2010 Higher urine volume results in additional renal iodine loss. Thyroid **20:**1391–1397.
16. Ittermann T, Volzke H, Krey A, Remer T, Heckmann M, Lange A, Kramer A, Below H 2019 Median urinary iodine concentration reflected sufficient iodine supply in neonates from Northeast Germany in 2005–2006. Eur J Nutr **58:** 1815–1820.
17. Bath SC, Rayman MP 2015 A review of the iodine status of UK pregnant women and its implications for the offspring. Environ Geochem Health **37:**619–629.
18. Zimmermann MB, Andersson M 2012 Assessment of iodine nutrition in populations: past, present, and future. Nutr Rev **70:**553–570.
19. Andersen S, Karmisholt J, Pedersen KM, Laurberg P 2008 Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. Br J Nutr **99:**813–818.

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Global epidemiology of hyperthyroidism and hypothyroidism

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Abstract | Thyroid hormones are essential for growth, neuronal development, reproduction and regulation of energy metabolism. Hypothyroidism and hyperthyroidism are common conditions with potentially devastating health consequences that affect all populations worldwide. Iodine nutrition is a key determinant of thyroid disease risk; however, other factors, such as ageing, smoking status, genetic susceptibility, ethnicity, endocrine disruptors and the advent of novel therapeutics, including immune checkpoint inhibitors, also influence thyroid disease epidemiology. In the developed world, the prevalence of undiagnosed thyroid disease is likely falling owing to widespread thyroid function testing and relatively low thresholds for treatment initiation. However, continued vigilance against iodine deficiency remains essential in developed countries, particularly in Europe. In this report, we review the global incidence and prevalence of hyperthyroidism and hypothyroidism, highlighting geographical differences and the effect of environmental factors, such as iodine supplementation, on these data. We also highlight the pressing need for detailed epidemiological surveys of thyroid dysfunction and iodine status in developing countries.

Thyroid hormones act on almost all nucleated cells and are essential for normal growth and energy metabolism[1]. Thyroid dysfunction is common, readily identifiable and easily treatable, but if undiagnosed or untreated, it can have profound adverse effects[2,3]. Despite an increase in thyroid disease awareness and the availability of sensitive laboratory assays for the measurement of thyroid hormones, cases of extreme thyroid dysfunction occasionally still occur[4,5]. Hypothyroidism and hyperthyroidism commonly arise from pathological processes within the thyroid gland (primary thyroid disease), although in rare cases, they can arise from disorders of the hypothalamus or pituitary (central hypothyroidism) or from peripheral causes, such as struma ovarii, or functional thyroid cancer metastases[6] (BOX 1).

In iodine-replete populations, thyroid dysfunction is most commonly due to thyroid autoimmunity. The autoimmune thyroid disorders comprise Graves disease, Hashimoto thyroiditis and post-partum thyroiditis, in which the presence of circulating thyroid-specific autoreactive antibodies is characteristic. Solitary or multiple autonomous nodule formation within the thyroid gland are also frequent causes of hyperthyroidism, while less common causes include thyroid gland inflammation or thyroiditis and adverse effects of medication, such as amiodarone and lithium. Both iodine deficiency and excess can result in hypothyroidism as well as hyperthyroidism.

The clinical presentation of thyroid disease is highly variable and often nonspecific; therefore, the diagnosis of thyroid dysfunction is predominantly based on biochemical confirmation. The complex inverse association between the pituitary-derived TSH and T_4 and T_3 renders TSH the more sensitive marker of thyroid status[7]. Accordingly, overt hypothyroidism is defined as TSH concentrations above the reference range and free T4 levels below the reference range, while subclinical hypothyroidism is defined as TSH levels above the reference range when levels of free T4 are within the population reference range[8]. Likewise, the reverse hormone pattern is applied in the definition of overt (low TSH and high T4) and subclinical hyperthyroidism (low TSH and normal T4).

Iodine is an integral component of thyroid hormones, but the global distribution of iodine is uneven, meaning some areas are iodine rich, while other are iodine deficient[9]. Over a billion people worldwide live in an iodine-deficient area, with the populations at greatest risk residing in remote mountainous regions, such as in Southeast Asia, South America and Central Africa[10]. Population differences in iodine nutrition have a major role in the global prevalence of thyroid dysfunction. Nodular thyroid disorders are more prevalent in areas where iodine deficiency is more common, while autoimmune thyroid disorders, including Hashimoto thyroiditis and Graves disease, occur more frequently in

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Key points

- Thyroid disease is a global health problem that can substantially impact well-being, particularly in pregnancy and childhood.
- In advanced economies, the prevalence of undiagnosed thyroid disease is falling owing to widespread thyroid function testing and relatively low thresholds for treatment initiation.
- Iodine nutrition remains a key determinant of thyroid function worldwide, and continued vigilance against the resurgence of iodine deficiency in previously sufficient regions remains essential.
- More studies are needed in developing countries, especially within Africa, to understand the role of ethnicity and iodine nutrition fluxes in current disease trends.

iodine-replete populations; however, a multitude of other risk factors, including genetic[11] and ethnic[12,13] susceptibility, sex[14], smoking status[15], alcohol consumption[9,16–18], presence of other autoimmune conditions[19], syndromic conditions[20] and exposure to some therapeutic drugs[21,22], also influence thyroid disease epidemiology[23] (TABLE 1). Lastly, the detection of thyroid dysfunction is driven by trends in clinical practice[24], and over the past 2 decades, progressive lowering of treatment thresholds, together[25] with increased thyroid function testing with sensitive assays, has led to a higher prevalence of so-called borderline or mild cases[25]. In this Review, we summarize the current epidemiology of hyperthyroidism and hypothyroidism and highlight global differences and environmental factors that influence disease occurrence.

Epidemiology of hyperthyroidism

The prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world[26,27] (TABLE 2). In 1977, the UK Whickham study reported that the incidence of hyperthyroidism was estimated at between 100 and 200 cases per 100,000 per year with a prevalence of 2.7% in women and 0.23% in men, taking into account both established and possible cases[28]. These figures were considerably higher than earlier retrospective data from the USA, which reported an incidence of 30 cases per 100,000 a year for Graves disease in the 1935–1967 period[29]. A 20-year follow-up of the Whickham cohort showed an ongoing incidence of 80 cases per 100,000 women per year[27,30]. In the 2002 United States National Health and Nutrition Examination Survey (NHANES III), overt hyperthyroidism was detected in 0.5% of the general population while 0.7% of the general population had subclinical hyperthyroidism[27] with an overall prevalence of 1.3%. Studies from several other countries, including Sweden[31,32], Denmark[33], Norway[34] and Japan[35], have all reported comparable incidence and prevalence rates. A meta-analysis of European studies estimated a mean prevalence rate of 0.75% for males and females combined and an incidence rate of 51 cases per 100,000 per year[26].

Global variation in the epidemiology of hyperthyroidism. The prevalence and incidence of thyroid dysfunction are difficult to compare across countries owing to differences in diagnostic thresholds, assay sensitivities, population selection and fluxes in iodine nutrition and population dynamics (TABLE 2). Furthermore, the precise causes of hyperthyroidism are not always reliably defined. The prevalence of overt hyperthyroidism is roughly similar in Europe and the United States (0.7% versus 0.5%)[26,27]. In Australia, a slightly lower prevalence of 0.3% was reported in 2016 for both overt and subclinical hyperthyroidism[36], while a 5-year incidence of hyperthyroidism was estimated at 0.5% in 2010 (REF. 37). In general, the incidence of hyperthyroidism corresponds to population iodine nutrition, with higher rates of hyperthyroidism occurring in iodine-deficient countries, mostly owing to an excess of nodular thyroid disease in elderly patients[38,39] (FIG. 1). For example, in Pescopagano, an iodine-deficient village of Southern Italy, the prevalence of hyperthyroidism was reported as 2.9% in 1999, mostly owing to an excess of cases of toxic nodular goitres[40]. This was more than double the observed prevalence of 0.2–1.3% in iodine-sufficient countries[26,27]. A cross-sectional study in China reported a higher prevalence of overt and subclinical hyperthyroidism in an iodine-sufficient area than in an iodine-deficient area (1.2% versus 1.0%; $P < 0.001$)[41]. These differences were, however, not observed either in China or in Japan when iodine-sufficient areas were compared with areas where the populace have an excessive iodine intake[35,42].

In Africa, the epidemiology of thyroid dysfunction has proved more challenging to monitor owing to a lack of comprehensive population-based studies[43]. Existing studies are largely sourced from hospital-based cohorts that exclude large segments of the rural population[44] and are therefore unlikely to be representative of the general population. A population study from several care homes for elderly individuals in Cape Town indicated a prevalence of 0.6% and 1.7% of hyperthyroidism and hypothyroidism, respectively, with two-thirds of cases being previously undiagnosed[45]. However, this study included only individuals who were white or of mixed descent and not black South Africans. In Johannesburg in 1981, the incidence of Graves disease was 5.5 per 100,000 per year[46], which was substantially lower than the rates of 50 per 100,000 reported in the UK[28,46]. However, a 60% rise in the incidence of Graves disease was observed over a 10-year period between 1974 and 1984 possibly owing to improvements in dietary iodine intake among urban migrants[46]. Recent hospital-based studies from Ghana show that contrary to earlier reports, Graves disease is not uncommon, comprising 54% of all cases of thyroid dysfunction[47], although this might reflect ascertainment bias. The prevalence of Graves disease in Ghana might be due to improvements in iodine nutrition. Studies conducted in the period following iodization in Ghana show marked increases in the incidence of both Graves disease and nodular disease, suggesting a role for improved diagnosis[48].

Aetiology and clinical phenotype. Graves disease is the most common cause of hyperthyroidism in iodine-replete populations[2]. Other common causes include toxic multinodular goitre and autonomously functioning thyroid adenoma[10]. Less common causes of

Box 1 | **Causes of hypothyroidism and hyperthyroidism**

Hypothyroidism

- Primary
  - Chronic autoimmune response (Hashimoto thyroiditis)
  - Iodine status: severe iodine deficiency or mild to severe iodine excess
  - Iatrogenic: radioiodine or surgery (usually to treat hyperthyroidism, goitre or thyroid cancer)
  - Genetic (including variations causing congenital hypothyroidism)
  - Drug-induced: therapeutics include amiodarone, lithium, monoclonal antibodies, sodium valproate (anti-epileptic), tyrosine kinase inhibitors and immune checkpoint inhibitors
  - Transient thyroiditis: post-partum (viral infection (De Quervain syndrome))
  - Thyroid infiltration: infectious, malignant (primary thyroid or metastatic) and other autoimmune conditions, such as sarcoidosis
- Secondary (central)
  - Hypothalamic failure and/or dysfunction
  - Pituitary dysfunction (macroadenoma and/or apoplexy)
  - Resistance to TSH or thyrotropin releasing hormone
  - Drug-induced (dopamine or somatostatins, for example)
- Extra-thyroidal
  - Consumptive hypothyroidism
  - Tissue-specific secondary to genetic mutations (for example, *THRα*, *THRβ* and *MCT8* (also known as *SLC16A2*)

Hyperthyroidism

- Primary
  - Increased stimulation, secondary to TSH receptor antibodies (Graves disease) and excess human chorionic gonadotropin secretion (hyperemesis gravidarum and trophoblastic tumours, such as choriocarcinoma or hydatidiform mole)
  - Autonomous thyroid function: toxic multinodular goitre, solitary toxic nodule and familial non-autoimmune hyperthyroidism
  - Excess release of stored thyroid hormone: autoimmune (silent or post-partum thyroiditis), infective (viral (De Quervain thyroiditis)), bacterial or fungal) pharmacological (amiodarone IFN-α) or radiation
  - Exposure to excess iodine known as the Jod–Basedow effect (from excess iodine intake including radiographic contrast)
- Secondary (central)
  - Inappropriate TSH secretion (TSH secreting pituitary adenoma or pituitary resistance to thyroid hormone)
- Extra-thyroidal
  - Excess intake of thyroid hormone (iatrogenic or factitious)
  - Ectopic thyroid hormone secretion (struma ovarii and functional thyroid cancer metastases)

hyperthyroidism are thyroiditis, pituitary TSH secreting adenoma and drug-induced hyperthyroidism[10]. In iodine-sufficient countries, Graves disease accounts for 70–80% of patients with hyperthyroidism[32], whereas in areas with iodine deficiency, Graves disease constitutes ~50% of all cases of hyperthyroidism, with the other half attributable to nodular thyroid disease[38]. These differences were elegantly demonstrated in epidemiological studies in the ethnically identical Northern European populations of Iceland and Denmark. The authors reported a high prevalence of Graves disease in Iceland, which is iodine sufficient, compared with a predominance of toxic multinodular goitre in Denmark, whose populace has a lower iodine intake[38].

The clinical phenotype in hyperthyroidism also shows geographical variation. Compared with patients with nodular disease, patients with Graves disease are younger, have higher thyroid hormone levels and are more likely to present with overt hyperthyroidism than subclinical hyperthyroidism[32]. Cardiovascular complications resulting from hyperthyroidism seem to be more prevalent in areas where toxic multinodular goitres are common, in part because patients with nodular disease are typically older[49]. Studies of sub-Saharan African patients with Graves disease show a disproportionate cardiovascular disease burden, which might be due to genetic susceptibility or to socio-economic factors that promote late presentation and poor disease control[50]. Ethnicity does seem to influence the risk of developing certain disease complications. For example, Graves ophthalmopathy is six times more common in white populations than in Asian populations[51]. Furthermore, the rare but serious complication of hyperthyroidism, thyrotoxic periodic paralysis, is markedly more common in Asian men. In China and Japan[52], periodic paralysis has an incidence of 2% compared with 0.2% in North America[53]. The genetic basis of this condition has been extensively studied, and variations in certain HLA haplotypes, such as DRw8, A2, Bw22, Aw19 and B17, have been identified in patients of Chinese or Japanese origin[54].

Graves disease. Graves disease is characterized by hyperthyroidism and diffuse goitre; ophthalmopathy, pretibial myxedema and thyroid achropachy can also be observed[55]. The pathogenesis of this enigmatic condition remains incompletely understood, but the central pathogenic event is the unregulated stimulation of the TSH receptor by autoreactive TSH receptor antibodies. Graves disease has been described throughout the globe[10] and predominantly affects women (the female:male ratio is 8:1), typically in their third to fifth decade of life[2]. An observational study from 2016 reported that the clinical phenotype of Graves disease, at least in Western countries, is becoming milder, presumably due to earlier diagnosis and treatment[56]. Graves ophthalmopathy occurs in 20–30% of patients, while pretibial myxedema is rarely observed[55]. A European survey from 2015 showed a declining incidence of severe thyroid eye disease, possibly owing to reduction in smoking rates together with more effective management of early stage disease in multidisciplinary clinic set-ups[57].

Toxic nodular disease. Toxic nodular goitre is the most frequent cause of thyrotoxicosis in elderly individuals, especially those in iodine-deficient areas[58]. Solitary toxic nodules are more common in women than in men, and some studies have reported a male:female ratio of 1:5. In areas where low iodine intake is prevalent, the incidence of toxic multinodular goitre is 18.0 cases per 100,000 per year compared with 1.5 cases per 100,000 per year in high-iodine-intake areas ($P < 0.001$)[38]. The incidence of solitary toxic nodules is similarly higher in low-iodine-intake areas than in high-intake areas (3.6 versus 1.6 per 100,000 per year; $P < 0.05$)[38]. In a stable iodine-sufficient area of Sweden, incidence rates for toxic multinodular goitre and solitary adenoma were 4.3 and 1.8 per 100,000 per year, respectively[32].

Thyrotoxicosis
The clinical state that results from too much thyroid hormone in the body. In the overwhelming majority of cases, this is due to excess production from the thyroid gland (hyperthyroidism).

Table 1 | **Risk factors for developing hypothyroidism and hyperthyroidism**

Risk factor	Hypothyroidism	Hyperthyroidism	Comment
Female sex	+	+	Sex hormones and the skewed inactivation of the X chromosome are suspected to be triggers for hypothyroidism and hyperthyroidism[26]
Iodine deficiency	+	+	Severe iodine deficiency can cause hypothyroidism and hyperthyroidism[170]
Iodine excess	+	+	Excess iodine status can trigger hyperthyroidism, typically in elderly individuals with long-standing thyroid nodules and hyperthyroidism[170]
Transition from iodine deficiency to sufficiency	+	+	Transition from iodine deficiency to sufficiency was associated with an increase in thyroperoxidase antibodies; one study reported an increase from 14.3% to 23.8%[145]. As a result, the incidence of overt hypothyroidism increased almost 20% from 38.3 per 100,000 per year at baseline to 47.2 per 100,000 per year[146]
Other autoimmune conditions	+	+	One study reported that another autoimmune disease was present in almost 10% of patients with Graves disease and in 15% of patients with Hashimoto's thyroiditis, with rheumatoid arthritis being the most common[19]
Genetic risk factors	n/a	NA	Both Graves disease and Hashimoto thyroiditis have genetic predispositions. Genome-wide association data have identified regions associated with thyroperoxidase antibody positivity[171] and thyroid disease[171,172]. Whole-genome sequencing might reveal novel insights[160]
Smoking	-	+	Current smoking increases the odds of Graves hyperthyroidism almost twofold and increases the risk of Graves ophthalmopathy almost eightfold[173]. Smokers also have a slower response during antithyroid drug treatment[174]. Smoking might protect against hypothyroidism as smokers have a 30–45% reduction in the odds of being thyroperoxidase antibody positive[175,176]. Current smokers had a 50% lower prevalence of subclinical hypothyroidism and a 40% lower prevalence of overt hypothyroidism than non-smokers[177]
Alcohol	-	NA	Moderate alcohol intake might be associated with a reduced risk of hypothyroidism[178]
Selenium deficiency	+	+	One study reported that patients with newly diagnosed Graves disease and hypothyroidism had lower selenium levels than the normal population. This finding was most pronounced in patients with Graves disease[18]
Drugs	+	+	Examples of drugs that can cause hyperthyroidism and hypothyroidism include amiodarone[21], lithium[22] and IFN-γ
Infections	NA	NA	Infectious agents have been associated with both autoimmune diseases and Graves disease[179]. The most well studied is *Yersinia enterocolitica*, although retroviruses have also been identified as a possible cause[16,179]
Syndromic conditions	+	NA	Almost 25% of patients in a large registry of patients with Down syndrome had thyroid disease, the most common being primary hypothyroidism[20]. The prevalence of hypothyroidism in Turner syndrome is approximately 13%[172], but the incidence increases substantially by the third decade of life

-, reduced risk; +, increased risk; NA, not applicable.

Thyroiditis. Thyroiditis is characterized by a self-limiting course of thyrotoxicosis, followed by hypothyroidism and then return to normal thyroid function[59]. The condition is slightly more common in females than males (female:male ratio of 1.5:1)[60], and permanent hypothyroidism occurs in 10–20% of cases[3] overall. Acute painful thyroiditis often presents following a respiratory tract infection[61], while painless thyroiditis can occur post-partum in up to 9% of otherwise healthy women[62]. Details of the epidemiology of painless thyroiditis are limited. One registry study in Minnesota reported an estimated incidence of 4.9 cases per 100,000 per year, with permanent hypothyroidism occurring in 15% of people[63]. Conversely, a Danish scintigraphy-based study estimated the incidence of painless thyroiditis to be only 0.49 cases per 100,000 per year[64]. Data from iodine-rich coastal areas of Japan suggested that as many as 10% of thyrotoxic patients had painless thyroiditis, in contrast to 2.4% of thyrotoxic patients in New York[65]. Some authors have argued that this variation might be due to increases in iodine intake in previously iodine-deficient regions[65], although ascertainment bias remains possible. A poll of endocrinologists indicated that silent thyroiditis was uncommon in Europe, Argentina and coastal areas of the United States but was more prevalent around the Great Lakes of the United States and Canada[66]. The reason for this trend is unclear but could be owing to rapid improvements in iodine intake in these previously iodine-deficient areas.

Silent thyroiditis
A self-limiting subacute disorder that results in temporary hyperthyroidism, usually followed by a brief period of hypothyroidism and then recovery of normal thyroid function. It most commonly occurs in females in the post-partum period.

Drug-induced hyperthyroidism. The iodine-rich compound amiodarone has been available for use in the clinic since the 1960s, and it remains widely prescribed as an anti-arrhythmic agent. Amiodarone-induced thyrotoxicosis is more common in iodine-deficient areas[67] and appears to be more common in men with a male:female ratio of up to 3:1. The reported regional prevalence of amiodarone-induced thyrotoxicosis is highly variable, ranging from 1% to 38%[67,68,69], with more detailed reported rates of 3% in North America[70] and 5.8% in Japan[71]. Clinicians must interpret these

Table 2 | **Incidence and prevalence of hyperthyroidism in iodine-sufficient and iodine-deficient countries**

Author, country and publication year	Study date	Sample no.	Age (years)	Female (%)	Iodine intake and UIC	Incidence per 10^5/year			Prevalence (%)		
						M	F	Total	M	F	Total
Iodine sufficient											
Tunbridge, UK, 1977 (REF. 28)	1972–1974	2,779	>18	54	811 nmol/24 h	NA	NA	NA	0.2	1.9	1.1
Mogensen, Denmark, 1980 (REF. 180)	1972–1974	439,756	>0	50	NA	8.7	46.5	27.6	NA	NA	NA
Berglund, Sweden, 1990 (REF. 181)	1970–1974	258,000	>0	52	NA	10.1	40.6	25.8	NA	NA	NA
Konno, Japan, 1993 (REF. 35)	1990–1991	4,110	Adult	29	NA	NA	NA	NA	0.3	0.5	0.3
Galofre, Spain, 1994 (REF. 182)	1990–1992	103,098	15–85	57	NA	6.5	89.1	52.4	NA	NA	NA
Berglund, Sweden, 1996 (REF. 31)	1988–1990	231,774	>0	53	NA	10.9	72.0	43	NA	NA	NA
Vanderpump, UK, 1995 (REF. 30)	1975–1994	1,877	38–93	56	102 µg/g Cr	0	80	53	0.2	3.9	2.5
Bjoro, Norway, 2000 (REF. 34)	1995–1997	94,009	>20	50	NA	NA	NA	NA	0.1	0.3	0.2
Canaris, USA, 2000 (REF. 104)	1995	24,337	>18	56	NA	NA	NA	NA	NA	NA	0.1
Hollowell, USA, 2002 (REF. 27)	1988–1994	13,344	>12	–	145 µg/l	NA	NA	NA	NA	NA	0.2
Volzke, Germany, 2003 (REF. 183)	1997–2001	3,941	20–79	48	12 µg/dl	NA	NA	NA	NA	NA	0.4
Flynn, UK, 2004 (REF. 105)	1993–1997	369,885	>0	–	NA	14	77	46	NA	NA	0.6
O'Leary, Australia, 2006 (REF. 184)	1981	2,115	16–89	50	NA	NA	NA	NA	0.1	0.2	0.1
Leese, UK, 2007 (REF. 185)	1994–2001	388,750	>0	52	NA	14	87	NA	0.2	1.3	0.8
Lucas, Spain, 2010 (REF. 186)	2002	1,124	18–74	56	150 µg/l	NA	NA	NA	0.2	0.2	0.2
Asvold, Norway, 2012 (REF. 102)	1995–2008	15,106	>20	67	NA	49.6	97.3	81.6	NA	NA	NA
Delshad, Iran, 2012 (REF. 187)	1999–2005	1,999	>20	61	NA	21	140	NA	NA	NA	NA
Unnikrishnan, India, 2013[a] (REF. 118)	2011	5,376	18–100	53.7	NA	NA	NA	NA	0.62	0.72	0.67
Sriphrapradang, Thailand, 2014 (REF. 188)	2009	2,545	≥14	46	NA	NA	NA	NA	NA	NA	0.94
Nystrom, Sweden, 2013 (REF. 32)	2003–2005	631,239	>0	NA	125 µg/l	NA	NA	27.6	NA	NA	NA
Valdes, Spain, 2017 (REF. 106)	2009–2010	4,554	18–93	58	117 µg/l	NA	NA	NA	NA	NA	0.4
Iodine deficient											
Kalk, South Africa, 1981 (REF. 46)	1974–1984	1,246,294	>15	48	NA	0.7	8.8	5.5	NA	NA	NA
Aghini-Lombardi, Italy, 1999 (REF. 40)	1995	992	>15	58	55 µg/l	NA	NA	NA	2.9	3.0	2.9
Knudsen, Denmark, 1999 (REF. 112)	1993–1994	2,613	41–71	49	70 µg/l	NA	NA	NA	0	1.2	0.6
Knudsen, Denmark, 2000 (REF. 33)	1997–1998	2,293	18–65	79	45 µg/l	NA	NA	NA	NA	NA	0.4
Knudsen, Denmark, 2000 (REF. 33)	1997–1998	2,067	18–65	79	61 µg/l	NA	NA	NA	NA	NA	0.8
Hoogendoorn, Netherlands, 2006 (REF. 189)	2002–2003	5,167	>18	54	NA	NA	NA	NA	0.2	0.6	0.4
Laurberg, Denmark, 2006 (REF. 39)	1997–1998	310,124	18–65	50	68 µg/l	36	149.1	92.9	NA	NA	NA
Laurberg, Denmark, 2006 (REF. 39)	1997–1998	225,707	18–65	53	53 µg/l	26.8	101.7	65.4	NA	NA	NA

Data are for cases of overt hyperthyroidism except where otherwise stated. Iodine status is based on reported status by authors; spaces are left blank where there are no data on incidence or prevalence or where the data are unclear from the report. [a]Study from eight cities with a wide mix of iodine status ranging from sufficient to deficient. Studies in specific population groups, such as children, pregnant women, specified comorbid states and unstable iodine nutrition are excluded. F, female; M, male; NA, not applicable; UIC, urinary iodine concentrations.

data with caution, however, as the precise definition of amiodarone-induced thyrotoxicosis and the frequency of patient monitoring are key determinants of the observed prevalence. Other drugs that cause thyrotoxicosis include IFN-α, lithium, tyrosine kinase inhibitors, highly active antiretroviral therapies, immune checkpoint mediators and the humanized monoclonal antibodies used in the treatment of multiple sclerosis[2,72]. Although these drugs can cause transient thyrotoxicosis through destructive thyroiditis, immune-modifying agents such as IFN-α, highly active antiretroviral therapies and alemtuzumab can also induce Graves disease through less well-defined immune reactivation mechanisms[73,74].

Subclinical hyperthyroidism. Precise estimates of the prevalence of subclinical hyperthyroidism are difficult to calculate because epidemiological studies use different diagnostic thresholds. Studies report figures ranging from 1% to 5%[75], although some of these studies include patients on levothyroxine[10]. Data from the NHANES

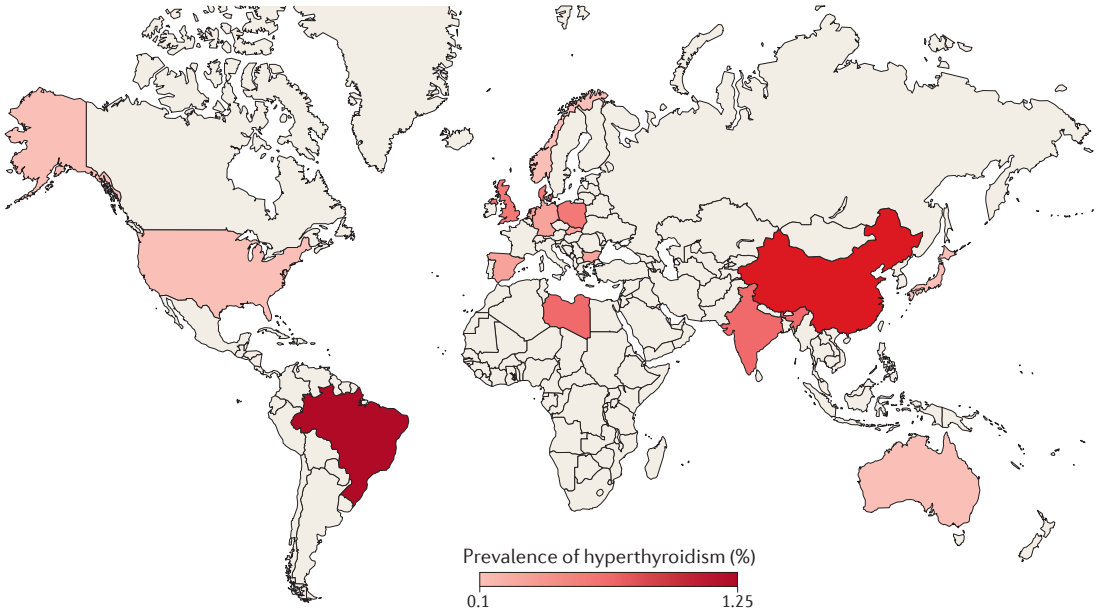

Fig. 1 | **Map of overt hyperthyroidism prevalence (selective populations used when representative data not available).** World map showing global prevalence of hyperthyroidism based on epidemiological samples. If multiple studies have been done on the prevalence of hyperthyroidism from one country, the median value was calculated. The deeper the shade of red, the higher the prevalence of hyperthyroidism. Countries in white represent no data available. This figure was created using Tableau software version 10.3.

III study suggest a bimodal peak at age 20–39 years and at >80 years of age[27]. The NHANES III study also showed that women were more likely to have subclinical hyperthyroidism. In addition, the authors reported that ethnicity influenced the risk of having subclinical hyperthyroidism with black Americans having a prevalence of 0.4%, Mexican Americans, 0.3% and white Americans, 0.1%[27]. In Asia, the prevalence of subclinical hyperthyroidism ranges between 0.43% to 3.9% of the general population[41]. Globally, the greatest risk factor for subclinical hyperthyroidism, aside from levothyroxine use, is iodine deficiency. The prevalence of subclinical hyperthyroidism increases from around 3% in iodine-sufficient areas[10] to 6–10% in iodine-deficient areas, largely owing to toxic nodular goitres[10]. In the UK, a TSH level of <0.1 mU/l was observed in 5.8% of patients who were treated with levothyroxine, while 10.2% of patients in the study had TSH levels of 0.1–0.5 mU/l. The authors also reported that women were more likely to be over-replaced as evidenced by a suppressed TSH. Data on the risk of progression from subclinical to overt hyperthyroidism are limited. In a Scottish database comprising 2,024 cases of subclinical hyperthyroidism, the vast majority of untreated patients did not progress to overt hyperthyroidism, and one-third of patients returned to normal thyroid status 7 years after initial diagnosis[76]. Other studies showed that patients with more severe grades of subclinical hyperthyroidism progressed more frequently to overt disease[77,78].

Iodine-induced hyperthyroidism. Iodine-induced hyperthyroidism, which is also known as the Jod–Basedow phenomenon, is more common in older persons with longstanding nodular goitre and in regions of chronic iodine deficiency where the populace is undergoing iodine supplementation[79]. Iodization programmes temporarily increase the risk of iodine-induced hyperthyroidism; elderly individuals who might have coexisting cardiac disease and also those with limited access to health care are principally at risk[79]. In addition to iodine supplementation, radiographic contrast agents can also cause iodine-induced hyperthyroidism. Individuals with pre-existing multinodular goitre or those from iodine-deficient areas are at greatest risk of iodine-induced hyperthyroidism following the administration of a radiographic contrast agent[80,81].

Hyperthyroidism in pregnancy. Thyrotoxicosis in pregnancy has an estimated incidence of 0.2% for overt thyrotoxicosis and 2.5% for subclinical thyrotoxicosis[82,83]. Data from the USA estimate the incidence to be 5.9 per 1000 pregnant women per year[84]. Women seem to be at greatest risk of hyperthyroidism in the first trimester[85]. Graves disease is the most common cause of thyrotoxicosis in pregnancy[2,82], although other causes, such as toxic nodules and goitres, can occur during gestation. The occurrence of hyperthyroidism in pregnancy might be overestimated, however, owing to the inclusion of cases of gestational thyrotoxicosis, a benign and transient disorder of pregnancy that typically occurs in the first trimester[2]. The management of thyrotoxicosis in pregnancy is complex and has to address the risk of maternal hyperthyroidism with that of fetal harm from transplacental transfer of maternal antibodies and thionamide drugs[86,87].

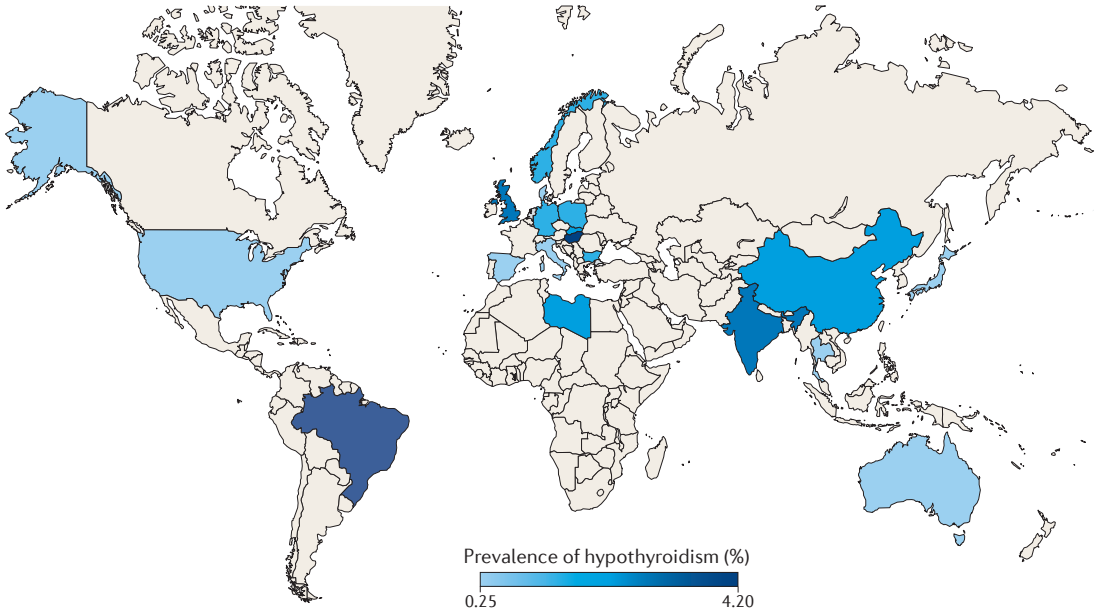

Fig. 2 | **Map of overt hypothyroidism prevalence (selective populations used when representative data not available).** World map showing global prevalence of hypothyroidism based on epidemiological samples. If multiple studies have been done on the prevalence of hypothyroidism from one country, the median value was calculated. The deeper the shade of blue, the higher the prevalence of hyperthyroidism. Countries in white represent no data available. This figure was created using Tableau software version 10.3.

Treatment of hyperthyroidism. Surprisingly, a substantial global variation exists in the treatment of hyperthyroidism. The choice of antithyroid drugs, radioiodine or surgery might have a modest impact on the epidemiology of hypothyroidism given that radioiodine and surgery ultimately result in permanent hypothyroidism[2]. Unlike in Europe, endocrinologists in the US have traditionally preferred radioiodine over antithyroid drugs. Two-thirds of American Thyroid Association respondents favoured the use of radioiodine as the primary treatment modality for Graves disease, whereas only 20% of members of European and UK thyroid societies said that they would use radioiodine as primary therapy[88]. In South Korea, 10% of practitioners recommended thyroidectomy as first-line treatment for Graves disease in contrast to other regions, such as Europe and the USA, where thyroidectomy is hardly used first line[88]. In African countries, owing to limited availability of radioisotopes, thyrotoxicosis is treated with antithyroid drugs or surgery[89].

Epidemiology of hypothyroidism

Hypothyroidism is common throughout the world and is particularly common in the UK (FIG. 2). Iodine deficiency and autoimmune disease (known as Hashimoto thyroiditis) account for the vast majority of cases of primary hypothyroidism[3]. A third of the world's population lives in iodine-deficient areas (FIG. 3a), and the devastating consequences of severe iodine deficiency on the neurological development of fetuses and children are well recognized[9]. Furthermore, the possible effects of less severe grades of iodine deficiency during pregnancy on offspring cognitive development are also becoming increasing recognized[90]. In addition, increased iodine demands and urinary excretion during pregnancy result in iodine deficiency in pregnant women despite sufficiency in the general adult population (FIG. 3b). Changes in diet and agricultural practices since the 1950s have led to the re-emergence of iodine deficiency in countries previously believed to be iodine sufficient, including some developed countries[91]. In Europe, 44% of school-age children still have insufficient iodine intake, and Italy seems to have become mildly iodine deficient in the past decade[92–99].

In iodine-sufficient countries, the prevalence of hypothyroidism ranges from 1% to 2%[10,100], rising to 7% in individuals aged between 85 and 89 years[101]. In the absence of age-specific reference ranges for TSH, an ageing population is likely to result in a higher prevalence of hypothyroidism. Hypothyroidism is approximately ten times more prevalent in women than men[10]. Data from Norway showed that the prevalence of untreated overt hypothyroidism was low at 0.1%, reflecting a fall of 84% from the 1990s. In the UK, the rate of new prescriptions of levothyroxine for primary hypothyroidism increased 1.74-fold from 2001 to 2009, which could be a result of the implementation of widespread thyroid function testing and a low threshold for treatment initiation.

Global variation in the epidemiology of hypothyroidism. The prevalence of overt hypothyroidism in the general population ranges from between 0.2% and 5.3% in Europe[102,103] and 0.3% and 3.7% in the USA[104], depending on the definition used and population studied (TABLE 3). Longitudinal studies from large UK cohorts report an incidence rate of spontaneous hypothyroidism of 3.5–5.0 per 1000 and 0.6–1.0 per 1000 in women and men, respectively[30,105]. A survey conducted in Spain reported

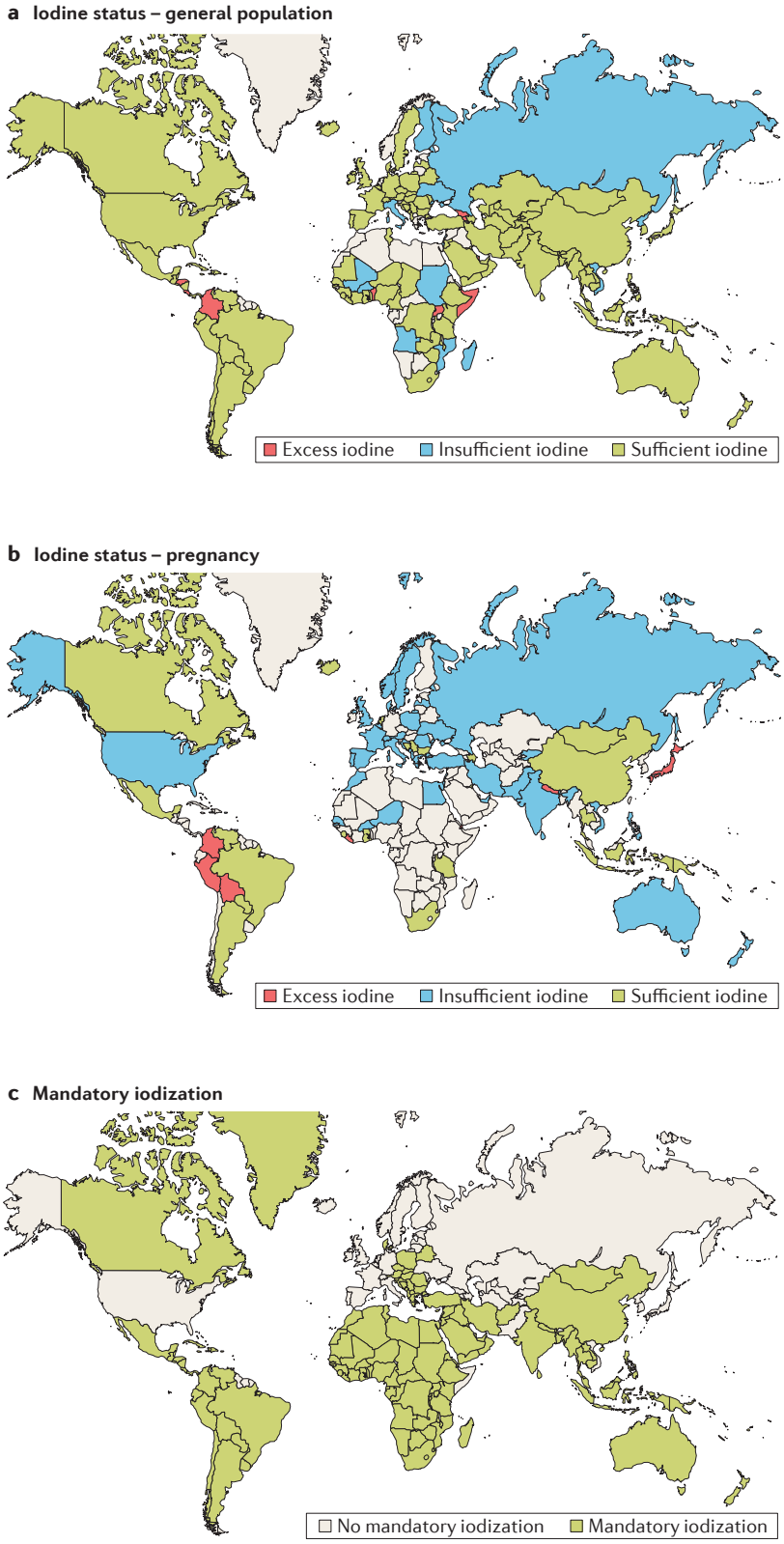

Fig. 3 | **Global iodine status and mandatory salt iodization. a** | World map showing global iodine status from general population studies based on the latest data (2017) from the Iodine Global Network[169]. Iodine status is defined as insufficient, sufficient or excessive. Countries in white represent no data available. **b** | World map showing global iodine status of pregnant women from studies based on the latest data (2017) from the Iodine Global Network[169]. **c** | World map showing countries that have mandatory salt iodization. This figure was created using Tableau software version 10.3.

a prevalence of treated hypothyroidism, untreated subclinical hypothyroidism and untreated clinical hypothyroidism of 4.2%, 4.6% and 0.3%, respectively[106]. A 2010 study from Australia reported the 5-year incidence of hypothyroidism in individuals aged >55 years was 0.5% and 4.2%, respectively[37], while the prevalence of overt and subclinical hypothyroidism was estimated at 0.5% and 5.0%, respectively[36]. The longest follow-up study is from the UK Whickham cohort[28,30], where the mean annual incidence of spontaneous hypothyroidism during a 20-year follow-up period was 35 cases per 10,000 surviving women and 6 cases per 10,000 surviving men[30]. Serum TSH levels of >5.2 mU/l and the presence of thyroid antibodies were associated with an increased risk of developing hypothyroidism with a positive interactive effect[30].

In the NHANES III study, the overall prevalence of hypothyroidism was 4.6%[27]. The prevalence was similar in white individuals and Hispanic people but was markedly lower in individuals of Afro-Caribbean descent (1.7%). A study from Brazil demonstrated similar differences with the highest prevalence of hypothyroidism seen in white individuals (1.6%) compared to people of black (0.59%) or mixed (1.27%) ancestry[13]. A separate study examined thyroid dysfunction in Brazilians of Japanese descent and found 0.8% of study participants had hypothyroidism and 8.9% had subclinical hypothyroidism[107]. Intriguingly, overall thyroid dysfunction rates were lower in a study based in Kasagi, Japan[108] despite the older age range of 56.9 (± 12.5) years versus 51.3 (± 9.0) years with a mean age of 51.3 ± 9.0 years in the study population. These differences suggest regional environmental differences exist with regards to development of hypothyroidism.

Data on the incidence of hypothyroidism in Middle Eastern countries are limited. One systematic review[109] evaluated 21 studies that addressed thyroid disease prevalence across ten Middle Eastern countries; however, there was wide heterogeneity in the populations studied, and most of the available studies were convenience samples sourced from cohorts of patients with diabetes mellitus, thyroid cancer or surgical and histopathological series, all of which include patients who are at high risk of thyroid dysfunction. In Tehran, an iodine-sufficient area of Iran, the annual incidence rates of subclinical and overt hypothyroidism were 7.62 and 2.0 per 1,000 persons, respectively[110], and in the same population, thyroid antibodies were detected in 16% of women and 8% of men[111], figures that are comparable to data from European populations[112].

The overall disease burden of hypothyroidism in sub-Saharan Africa, based on largely hospital clinic data, is predicted to be minimal (or even rare) and substantially lower than the prevalence found in African Americans. In 2007, following a small hospital study in Lagos, Nigeria, the authors reported that the majority of patients seen in a thyroid clinic had hyperthyroidism[113]. In this study, Hashimoto thyroiditis was diagnosed in only 6% of patients, and positive thyroid peroxidase antibodies were detected in 4% of the healthy population[113]. However, the significant referral bias and exclusion of large numbers of the general population should

Table 3 | **Incidence and prevalence of hypothyroidism in iodine-sufficient and iodine-deficient countries**

Author, country and publication year	Study date	Sample no. (ethnicity)	Age (years)	Female (%)	Iodine intake and UIC	Incidence per 10^5 per year			Prevalence (%)		
						M	F	Total	M	F	Total
Iodine sufficient											
Tunbridge, UK, 1977 (REF. 28)	1972–1974	2,779	>18	54	811 nmol/24 h	NA	NA	NA	0.1	1.4	1.8
Konno, Japan, 1993 (REF. 35)	1990–1991	4,110	Adult	29	NA	NA	NA	NA	0.68	3.13	NA
Galofre, Spain, 1994 (REF. 182)	1990–1992	103,098	15–85	57	NA	10.9	73.4	45.6	NA	NA	NA
Vanderpump, UK, 1995 (REF. 30)	1975–1994	1,877	38–93	56	102 µg/g Cr	60	350	243	1.3	9.3	5.8
Bjoro, Norway, 2000 (REF. 34)	1995–1997	94,009	>20	50	NA	NA	NA	NA	0.4	0.8	0.7
Canaris, USA, 2000 (REF. 104)	1995	24,337	>18	56	NA	NA	NA	NA	NA	NA	0.4
Hollowell, USA, 2002 (REF. 27)	1988–1994	13,344	>12	–	145 µg/l	NA	NA	NA	NA	NA	0.3
Volzke, Germany, 2003 (REF. 183)	1997–2001	3,941	20–79	48	12 µg/dl	NA	NA	NA	NA	NA	0.7
Flynn, UK, 2004 (REF. 105)	1993–1997	369,885	>0	NA	NA	88	498	297	–	–	3.0
O' Leary, Australia, 2006 (REF. 184)	1981	2,115	16–89	50	NA	NA	NA	NA	0.37	0.65	0.54
Teng[a], China (total), 2006 (REF. 117)	1999	3,761 (total)	≥18	69	NA	NA	NA	NA	NA	NA	NA
Teng[a], China (excess), 2006 (REF. 117)	1999	1,074	≥18	NA	NA	NA	NA	NA	NA	NA	2.0
Teng[a], China (sufficient), 2006 (REF. 117)	1999	1,584	≥18	NA	NA	NA	NA	NA	NA	NA	0.9
Sichieri, Brazil, 2007 (REF. 13)	2004–2005	528 (white)	≥35	100	NA	NA	NA	NA	NA	1.6	NA
Sichieri, Brazil, 2007 (REF. 13)	2004–2005	490 (mixed)	NA	NA	NA	NA	NA	NA	NA	1.27	NA
Sichieri, Brazil, 2007 (REF. 13)	2004–2005	202 (black)	NA	NA	NA	NA	NA	NA	NA	0.59	NA
Leese, UK, 2007 (REF. 185)	1994–2001	388,750	>0	52	NA	101.0	457.0	NA	1.0	5.5	3.0
Kasagi, Japan, 2009 (REF. 108)	2005–2006	1,818	51.3 ± 9.0	56	NA	NA	NA	NA	0.16	0.50	0.66
Lucas, Spain, 2010 (REF. 186)	2002	1,124	18–74	56	150 µg/l	NA	NA	NA	0	0.5	0.2
Sgarbi, Brazil, 2010 (REF. 107)	1999–2000	1,110	>30	53	NA	NA	NA	NA	0.4	0.4	0.8
Asvold, Norway, 2012 (REF. 102)	1995–2008	15,106	>20	67	NA	113	317	249	NA	NA	NA
Marwaha, India, 2012 (REF. 190)	2007–2010	4,402	18–90	63	NA	NA	NA	NA	NA	NA	4.2
Delshad, Iran, 2012 (REF. 187)	1999–2005	1,999	>20	61	NA	21	28	NA	NA	NA	-
Unnikrishnan, India, 2013[a] (REF. 118)	2011	5,376	18–100	54	NA	NA	NA	NA	NA	NA	10.95
Sriphrapradang, Thailand, 2013 (REF. 188)	2009	2,545	≥14	NA	NA	NA	NA	NA	NA	NA	0.74
Iodine deficient											
Laurberg, Denmark, 1999 (REF. 191)	24 months	569,108	>0	51	60 µg/day	3.6	22.9	13.5	NA	NA	NA
Aghini-Lombardi, Italy, 1999 (REF. 40)	1995	992	>15	58	55 µg/l	NA	NA	NA	0	0.3	0.2
Knudsen, Denmark, 1999, (REF. 112)	1993–1994	2,613	41–71	49	70 µg/l	NA	NA	NA	0.2	0.5	0.3
Knudsen, Denmark, 2000, (REF. 33)	1997–1998	2,293	18–65	79	45 µg/l	NA	NA	NA	NA	NA	0.2
Knudsen, Denmark, 2000 (REF. 33)	1997–1998	2,067	18–65	79	61 µg/l	NA	NA	NA	NA	NA	0.6
Hoogendoorn, 2006, Netherlands (REF. 189)	2002–2003	5,167	>18	54	NA	NA	NA	NA	0.2	0.6	0.4
Laurberg, Denmark, 2006 (REF. 39)	1997–1998	310,124	18–65	50	68 µg/l	9.4	43.5	26.5	NA	NA	NA
Laurberg, Denmark, 2006 (REF. 39)	1997–1998	225,707	18–65	53	53 µg/l	17.3	60.6	40.1	NA	NA	NA
Teng[b], China (deficient), 2006 (REF. 117)	1999	1,103	≥18	NA	NA	NA	NA	NA	NA	NA	0.3
Du, China (mildly deficient), 2014 (REF. 41)	NA	667	≥18	71	NA	NA	NA	NA	0.15	0.90	1.05

Data are for cases of overt hypothyroidism except where otherwise stated. Iodine status is based on reported status by authors; spaces are left blank where there are no data on incidence or prevalence or where the data are unclear from the report. F, female; M, male; NA, not applicable; UIC, urinary iodine concentrations. [a]Same study population, studied at 5-year and 11-year intervals post-iodization. Data in follow-up available on excess replacement because in some individuals excess levels were recorded (median in this group, 651 µg/l).[b]Data from eight cities with a wide mix of iodine status from sufficient to deficient. Studies in specific population groups such as children, pregnant women, specified comorbid states and unstable iodine nutrition are excluded.

lead clinicians to question the generalizability of these figures. In 2012, thyroid dysfunction was reported in African patients, as well as Asian patients with HIV who were taking multidrug-resistant treatment regimens for tuberculosis[114,115]. Patients in these cohorts have been prescribed agents like ethionamide that inhibit thyroid hormone synthesis[114].

Over the past decade in China, the prevalence of subclinical hypothyroidism has increased (16.7% versus 3.22%, along with the proportion of the thyroid peroxidase antibody positive population (11.5% versus 9.81%)[116], reflecting the transition to iodine sufficiency[116,117]. Similar to the data from Chinese cohorts, a large cross-sectional multicity study in India reported in 2013 remarkably high rates of hypothyroidism (10%), although this study included self-reported cases[118]. Furthermore, regional variations were reported in India, with higher rates of hypothyroidism in inland than in coastal regions[118]. Among all cities, Kolkata recorded the highest prevalence of hypothyroidism (21.67%). Cities located in the inland regions of India (Delhi, Ahmedabad, Kolkata, Bangalore and Hyderabad) reported a significantly higher prevalence of hypothyroidism (11.73%) than those in the coastal areas (Mumbai, Chennai and Goa) (9.45%; $P = 0.01$)[118].

There is now a growing appreciation in India that hypothyroidism represents a substantial health problem despite extensive universal salt iodization[119]. The prevalence appears to be substantially higher than in Europe and the USA, and while genetic and iodine factors are likely to play a substantial part, other factors, including high levels of endocrine disruptors, have been postulated to have an impact[119].

Hypothyroidism in pregnancy. In iodine-sufficient areas, the prevalence of hypothyroidism in pregnancy is ~2%[83,120]. Optimal control of thyroid status is essential for both obstetric and offspring outcomes, although the precise treatment thresholds are unclear[121]. Correction of both overt hypothyroidism and hyperthyroidism dramatically reduces the risk of fetal loss and preterm birth[122,123]. Subclinical hypothyroidism before 20 weeks of pregnancy is associated with an increased risk of miscarriage[124], and isolated hypothyroxinaemia (which is usually defined as free T4 in lowest 2.5th centile with normal TSH) is associated with adverse pregnancy outcomes, including prematurity[125]. Randomized controlled trials in women with gestational subclinical hypothyroidism and isolated hypothyroxinaemia have failed to show benefits of levothyroxine therapy on the IQ of the offspring[126,127] or obstetric outcomes[127]. In these trials, however, levothyroxine was initiated from the end of the first trimester of pregnancy after the early critical phase of fetal brain development. Universal thyroid screening in pregnancy is therefore contentious, although it has been shown to be cost-effective in analytical economic models[128].

Congenital hypothyroidism. Congenital hypothyroidism is one of the most common treatable causes of mental retardation[129]. Until 2007, congenital hypothyroidism was estimated to affect approximately one newborn baby in 3500–4000 births[130], but over the past decade, several screening programmes have reported an increase in prevalence. Analysis of data from the USA identified a near doubling of the incidence of congenital hypothyroidism in a 15-year period from 1987 at 1 in 3,985 to 1 in 2,273 in 2002. Another group reported a similar change in New Zealand[131]. Some of this increase is due to changes in the ethnicity of the populations studied, although lowering of the TSH cut-off has also contributed[132]. Despite the clear advantages of birth screening programmes, it is estimated that only ~29.3% of the world's birth population is screened for congenital hypothyroidism[133].

Drug-induced hypothyroidism. Several drugs cause hypothyroidism. Until 2017, the most notable were lithium and amiodarone and tyrosine kinase inhibitors. Lithium therapy causes overt hypothyroidism in 5–15% of patients treated[134]. In one study of laboratory data, the use of lithium increased the risk of hypothyroidism by more than twofold (OR = 2.31; 95% CI 2.05, 2.60; $P < 0.0001$)[22]. Amiodarone-induced hypothyroidism may be more common than amiodarone-induced thyrotoxicosis in iodine-sufficient areas[67,135], with amiodarone-induced hypothyroidism occurring in 6.9–22% of patients in iodine-sufficient areas and amiodarone-induced thyrotoxicosis occurring in between 2% and 12.1% of patients, although this difference may be explained by the heterogeneity between studies[67].

Immune checkpoint inhibitors, which can be prescribed as single agents or in combination, have emerged as key treatments in managing advanced cancers. The key immune checkpoint inhibitors are antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA4), such as ipilimumab; programmed cell death protein 1 (PD1), such as nivolumab and pembrolizumab; and anti-PD1 ligand molecules (PDL1 and PDL2), such as atezolizumab and durvalumab. These agents have been approved for a variety of cancers, including melanoma, non-small-cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancers[72].

Immune checkpoint inhibitors reactivate the immune system against cancer cells but can also induce autoimmune adverse effects that have a preponderance for the hypothalamic–pituitary–thyroid axis[72]. While these may not substantially increase the incidence of thyroid disease, the complexity of these patients may result in a substantial future addition to patients attending specialist thyroid clinics as oncologists, and general practitioners may lack the necessary thyroid expertise.

Patients taking immune checkpoint inhibitors can develop primary or secondary hypothyroidism and primary hyperthyroidism. Secondary hypothyroidism is more common in patients taking anti-CTLA4 antibodies, whereas primary hypothyroidism is observed more frequently in patients taking anti-PD1 and anti-PDL1 monoclonal antibodies[72]. Hypothyroidism has been reported to occur in between 1.5% and 6.8% of patients on ipilimumab, 9% and 10.8% of patients on nivolumab and 5.5% and 9.6% of patients on durvalumab[72]. In combination therapy with nivolumab and

ipilimumab, hypothyrodism is higher still, occurring in 4–27%[72]. A 2017 meta-analysis[73] of 38 randomized controlled trials comprising 7,551 patients taking ipilimumab (a CTLA4 inhibitor) as a baseline reported that individuals who received a combination therapy of PD1 plus CTLA4 inhibitors had the highest odds of developing hypothyroidism (OR = 3.81; 95% CI 2.10, 6.91), hyperthyroidism (OR 4.27; 95% CI 2.05, 8.90) and hypophysitis (OR 2.2; 95% CI 1.39, 3.60). The authors also reported that patients taking PD1 inhibitors had a higher risk of developing hypothyroidism (OR = 1.89; 95% CI 1.17, 3.05) than those taking ipilimumab.

Alemtuzumab, a novel treatment for multiple sclerosis, has also been associated with a high prevalence of hypothyroidism[136]. Tyrosine kinase inhibitors can result in an increased risk of hypothyroidism with 27% of treated patients requiring levothyroxine[137] during their treatment.

Iodine-induced hypothyroidism. The underlying mechanism of iodine-induced hypothyroidism is not well understood, but data suggest that it is attributed to a failure of thyroid adaptive mechanisms to an acute iodide load (known as the Wolff–Chaikoff effect)[138]. Common sources of excess iodine include supplementation, diet, iodinated contrast agents and medication[81,139]. In the next section, we present a discussion of the effect of iodine fortification on the epidemiology of hypothyroidism and hyperthyroidism.

Effect of iodine fortification

Over the past 25 years, many countries across the globe have introduced mandatory salt iodization programmes (FIG. 3c), which have reduced the number of iodine-deficient countries dramatically. It is noteworthy that Europe has been slow to introduce mandatory salt iodization. As of 2016, 110 countries are now classified as having optimal iodine intake, while insufficient iodine intake persists in only 19 countries[140]. Iodine fortification of all food-grade salt is now mandated in ~120 countries[141], although voluntary fortification programmes do not allow for enforcement. Moreover, these initiatives require regular monitoring to ensure that fortification programmes meet changing demands given the adverse outcomes of oversupply or undersupply of iodine. In Europe, few countries have regular monitoring[9], and countries that are engaged in regular studies on iodine fortification are using heterogeneous methods and outcomes, which prohibit an appropriate comparison within meta-analyses.

Some studies with longitudinal data have surveyed the occurrence of thyroid dysfunction in relation to national iodization programmes (TABLE 4). These studies show variable trends that depend on pre-existing population iodine status, magnitude of iodization and survey methodology. There is well-documented evidence of an increase in the frequency of thyroid autoimmunity following iodization programmes[23,43,117,142]. The mechanism of this phenomenon is complex, but could be due to iodization of thyroglobulin[143], which enhances immunogenicity through altered epitope expression[144]. An analysis of fortification programmes in Denmark revealed that even cautious iodization programmes are associated with an increase in thyroperoxidase antibodies. The data from this particular study showed that the incidence of thyroperoxidase antibodies in the study population increased from 14.3% and 23.8%[145]. As a result, the incidence of overt hypothyroidism increased almost 20% from 38.3 per 100,000 per year at baseline to 47.2 per 100,000 per year, an increase that was most marked in young and middle-aged individuals in an area of moderate iodine deficiency[146].

A study in Poland showed that hypothyroidism occurs more frequently after a mandatory iodine prophylaxis (2.1% versus 1.4% in females and 0.3% versus 0% in males)[147]. In an elderly Icelandic population with relatively high iodine intake, the prevalence of high serum TSH concentrations (>4 mU/l) was 18%, whereas in individuals with low iodine intake residing in Jutland, Denmark, high serum TSH levels were prevalent in 3.8% of the participants, showing that ingestion of smaller quantities of iodine could affect thyroid function in a population at large[148]. Similar to these findings, the prevalence of non-autoimmune hypothyroidism was 12.1% in coastal areas of the Hokkaido Islands, Japan, compared with 2.3% in noncoastal areas, owing to the high iodine intake from seaweed (kelp) consumption[149]. In a 5-year follow-up study in China, the prevalence of subclinical hypothyroidism and thyroid autoimmunity was highest in areas with excessive iodine nutrition status[117]. However, data from Tasmania[150], Bangladesh[151] and Italy[152] did not show an increase in hypothyroidism following iodine fortification, although a minimal rise in serum TSH (from 1.37 mU/l to 1.61 mU/l) was observed in Italy[152].

One offshoot of iodization is the risk of thyrotoxicosis secondary to excessive iodization. A growing number of countries, ten as of 2016, are now classified as having excessive iodine intake status[140]. In the past, cases of iodine-induced thyrotoxicosis were observed following salt iodization programmes or increases in dietary iodine intake[153–156]. The most notable of these occurred in the Tasmanian state of Australia[155], in Harare, Zimbabwe[154], and in Kivu, Northern Zaire[153]. In these areas, increases in cases of toxic nodular goitres were observed in the period after iodization, with fatalities resulting from cardiovascular complications in some areas[153]. Elderly individuals with long-standing nodular goitres are particularly susceptible to complications of iodine fortification programmes; however, iodine-induced thyrotoxicosis is transient and limited to instances of sharp increases in iodine intake in areas of long-standing iodine deficiency or in urban migrants who relocate to iodine-sufficient areas from iodine-deficient areas[43]. A chronic state of excessive iodine nutrition has raised concerns in some sub-Saharan African countries[9], and excess iodine nutrition has been reported among refugees and displaced populations within the region who rely on iodized salt sourced from food aid from regional governments and international aid agencies[157,158]. While these important observations call for continued vigilance of iodine supplementation programmes, they should not deter from the goal, which is the eradication of iodine deficiency.

Table 4 | **Longitudinal studies of iodine supplementation and frequency of hyperthyroidism and hypothyroidism**

Author, year and country (region)	Sample no.	Age (years)	Female (%)	Iodization year	Form of iodization	MUI (μg/l)	Incidence of hypothyroidism		Incidence of hyperthyroidism	
							Pre-iodization	Post-iodization	Pre-iodization	Post-iodization
Galofre, Spain, 1994 (REF. 192)	103,098	15–85	57	1985	KI 60 mg/kg salt	NA	NA	NA	$3.10/10^5$	$7.68/10^5$
Yang, China (Panshan),2002 (REF. 193)	1,103	14–88	65	1996	USI	84	NA	NA	$28/10^5$	$81/10^5$
Yang, China (Zhangwu), 2002 (REF. 193)	1,584	14–95	69	1996	USI	243	NA	NA	$23/10^5$	$36/10^5$
Yang, China (Huanghua),2002 (REF. 193)	1,074	14–79	66	1996	USI	651	NA	NA	$35/10^5$	$37/10^5$
Teng, China (Panshan),2006 (REF. 117)	884	19–80	68	1996	USI	88	NA	1.2%	NA	5.3%
Teng, China (Zhangwu), 2006 (REF. 117)	1,270	19–84	70	1996	USI	214	NA	3.8%	NA	5.9%
Teng, China (Huanghua), 2006 (REF. 117)	1,074	19–83	69	1996	USI	634	NA	8.1%	NA	2.3%
Golkowski, Poland, 2007 (REF. 194)	1,424	16+	66	1997	KI 30 mg/kg salt	112	-	-	4.8%	6.5%
Pedersen, Denmark (Aalborg), 2007 (REF. 146)	310,124	>0	NS	1998	8–13 ppm	53	$30/10^5$	$40/10^5$	NA	NA
Pedersen, Denmark (Copenhagen), 2007 (REF. 146)	225,707	>0	NS	1998	8–13 ppm	68	$52/10^5$	$57/10^5$	NA	NA
Heydarian, Iran, 2007 (REF. 195)	1,891	>20	NA	1994	KI 40 mg/kg salt	–	$328/10^5$	$25.2/10^5$	$88/10^5$	$63/10^5$
Cerqueira, Denmark (Western region), 2011 (REF. 299)	2,920,000 (5,300,000 total)	>0	NS	1998	8–13 ppm	53	$72/10^5$	$126/10^5$	NA	NA
Cerqueira, Denmark (Eastern region), 2011 (REF. 196)	2,380,000 (5,300,000 total)	>0	NS	1998	8–13 ppm	68	$87/10^5$	$163/10^5$	NA	NA
A-Lombardi, Italy, 2013 (REF. 197)	2,289	>1	64	2005	KI 30 mg/kg salt	55	2.8%	5.0%	2.1%	1.6%
Tammaro, Italy, 2016 (REF. 152)	7,976	NA	85	2005	NA	NA	NA	NA	2.5%	2.1%
Hong, Australia, 2017 (REF. 150)	389,910	45 ± 20	59	2001	Iodized bread	75	–	60% fall[a]	–	62% fall[a]

Prevalence figures are in percentages and incidence rates are in cases/10^5. Figures represent overt and subclinical thyroid dysfunction. Age is in range or mean ± standard deviation. KI, potassium iodide; MUI, median urinary iodine concentration at onset of programme; NA, not applicable; NS, not stated; ppm, parts per million; USI, universal salt iodization. [a]Fall in the incidence of overt thyroid dysfunction from 1995 to 2013.

Conclusion

In this Review, we have summarized the current epidemiology of hypothyroidism and hyperthyroidism and examined factors that affect the prevalence of thyroid disease. In iodine-sufficient areas, the majority of thyroid dysfunction is due to thyroid autoimmunity, and data from Europe and other parts of the world have revealed the influence of variation in iodine status and the impact of iodine supplementation on the epidemiology of thyroid dysfunction[9,26,91]. Other factors that can affect the epidemiology of thyroid disease are the increasingly widespread use of thyroid function testing[102], lowering of treatment thresholds and introduction of novel therapeutic agents that can affect thyroid function. In addition, we have demonstrated striking geographical and ethnic differences in thyroid disease epidemiology. In African-American populations, the frequency of hypothyroidism appears to be lower than in white individuals[27]. Careful reanalysis of data from the NHANES III study indicates that non-Hispanic black individuals had a 54% lower risk of hypothyroidism than non-Hispanic white individuals, but non-Hispanic black individuals had over a threefold higher risk of hyperthyroidism[12]. Data from Brazil show a similar pattern, with black individuals having the lowest prevalence of hypothyroidism and those of dual heritage and white individuals having a higher prevalence[13] (TABLE 3). In India, striking regional variations in the prevalence of hypothyroidism have been reported[118,159], which raises the need for the standardization of assay methods and region-specific and population-specific reference ranges.

A greater understanding of the genetic variants responsible for variation in TSH and thyroid hormone levels is emerging, but, to date, only a small proportion (<10%) of the genetic architecture has been explained[11,160]. Variants have been identified that increase the risk of Graves disease[11,161] and thyroperoxidase antibody positivity[11]. An increased understanding of the genetic architecture is required, particularly in populations of individuals who are not white. An analysis of differences in risk variants identified in different populations would provide improved insight into the variations in thyroid disease globally and might explain borderline abnormalities in serum TSH levels. Currently, many individuals with modest abnormalities in TSH levels are started on treatment[25], but such individuals would have spontaneously reverted to normal without intervention[162]. A 2017 trial of thyroid hormone therapy for older adults with subclinical hypothyroidism, the TRUST trial[163], identified that up to 60% of potentially eligible elderly individuals with an elevated TSH had returned to euthyroidism when reassessed for the trial. The clinical significance of subclinical thyroid dysfunction, or of variations in thyroid hormones within the laboratory reference range, remains contentious[164–167] and beyond the scope of this Review. However, in the future, genetic risk factor profiles might augment other risk factors in stratifying individuals with borderline abnormalities in serum TSH levels[160].

There is still considerable controversy as to whether healthy adults in iodine-sufficient areas will benefit from screening for thyroid disease. Targeted screening for thyroid dysfunction in pregnancy is commonplace, and universal thyroid screening in pregnancy continues to generate impassioned debate[121]. The prevalence of unsuspected thyroid disease is low in developed countries, but a substantial proportion of individuals will have evidence of minor thyroid dysfunction[102]. At present, however, no appropriately powered prospective, randomized interventional trial that is controlled and double-blinded of either levothyroxine therapy for subclinical hypothyroidism or antithyroid therapy for subclinical hyperthyroidism has been conducted in healthy adults <40 years of age in the general population, although data are emerging for individuals >65 years of age[167].

It is striking that up to 50% of cases of subclinical hyperthyroidism have arisen from levothyroxine treatment, especially because the threshold for treatment initiation has fallen since 2000 (REFS 25,168). Studies on the incidence and prevalence of thyroid disease are urgently needed in the developed world, in addition to the consequences of current prescribing practice. We also need greater clarification of treatment thresholds in pregnancy as well as in the general population. Ongoing data capture of the prevalence and incidence of thyroid disease is still required in the developing world, especially in areas where there are fluxes in population iodine nutrition. In the developed world, endeavours such as EUthyroid, a collaborative venture promoting monitoring of iodine status and its consequences on thyroid disease epidemiology, will be crucial. Such initiatives will need to be supported by appropriate randomized controlled trials in subclinical thyroid disease and in optimal management of hypothyroidism.

1. Dumont, J. et al. Ontogeny, anatomy, metabolism and physiology of the thyroid. *Thyroid Disease Manager* https://www.thyroidmanager.org/chapter/ontogeny-anatomy-metabolism-and-physiology-of-the-thyroid (2011).
2. De Leo, S., Lee, S. Y. & Braverman, L. E. Hyperthyroidism. *Lancet* **388**, 906–918 (2016).
3. Chaker, L., Bianco, A. C., Jonklaas, J. & Peeters, R. P. Hypothyroidism. *Lancet* **390**, 1550–1562 (2017).
4. Rice, S. P., Boregowda, K., Williams, M. T., Morris, G. C. & Okosieme, O. E. A. Welsh-sparing dysphasia. *Lancet* **382**, 1608 (2013).
5. Taylor, P. N. et al. Weekly intramuscular injection of levothyroxine following myxoedema: a practical solution to an old crisis. *Case Rep. Endocrinol.* **2015**, 169194 (2015).
6. Persani, L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J. Clin. Endocrinol. Metab.* **97**, 3068–3078 (2012).
7. Hadlow, N. C. et al. The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. *J. Clin. Endocrinol. Metab.* **98**, 2936–2943 (2013).
8. Pearce, S. H. et al. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur. Thyroid J.* **2**, 215–228 (2013).
9. Zimmermann, M. B. Iodine deficiency. *Endocr. Rev.* **30**, 376–408 (2009).
10. Vanderpump, M. P. The epidemiology of thyroid disease. *Br. Med. Bull.* **99**, 39–51 (2011).
11. Medici, M. et al. Identification of novel genetic loci associated with thyroid peroxidase antibodies and clinical thyroid disease. *PLoS Genet.* **10**, e1004123 (2014).
12. Aoki, Y. et al. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid* **17**, 1211–1223 (2007).
13. Sichieri, R. et al. Low prevalence of hypothyroidism among black and Mulatto people in a population-based study of Brazilian women. *Clin. Endocrinol.* **66**, 803–807 (2007).
14. De Groot, L. et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **97**, 2543–2565 (2012).
15. Wiersinga, W. M. Smoking and thyroid. *Clin. Endocrinol.* **79**, 145–151 (2013).
16. Wiersinga, W. M. Clinical relevance of environmental factors in the pathogenesis of autoimmune thyroid disease. *Endocrinol. Metab.* **31**, 213–222 (2016).
17. Preau, L., Fini, J. B., Morvan-Dubois, G. & Demeneix, B. Thyroid hormone signaling during early neurogenesis and its significance as a vulnerable window for endocrine disruption. *Biochim. Biophys. Acta* **1849**, 112–121 (2015).
18. Bulow Pedersen, I. et al. Serum selenium is low in newly diagnosed Graves' disease: a population-based study. *Clin. Endocrinol.* **79**, 584–590 (2013).
19. Boelaert, K. et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am. J. Med.* **123**, 183.e1–183.e9 (2010).
20. Pierce, M. J., LaFranchi, S. H. & Pinter, J. D. Characterization of thyroid abnormalities in a large cohort of children with Down syndrome. *Hormone Res. Paediatr.* **87**, 170–178 (2017).
21. Bartalena, L. et al. Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin. Endocrinol.* **61**, 494–502 (2004).
22. Shine, B., McKnight, R. F., Leaver, L. & Geddes, J. R. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet* **386**, 461–468 (2015).
23. Laurberg, P. et al. Iodine intake as a determinant of thyroid disorders in populations. Best practice and research. *Clin. Endocrinol. Metab.* **24**, 13–27 (2010).
24. Bould, H. et al. Investigation of thyroid dysfunction is more likely in patients with high psychological morbidity. *Fam. Pract.* **29**, 163–167 (2012).
25. Taylor, P. N. et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern. Med.* **174**, 32–39 (2014).
26. Garmendia Madariaga, A., Santos Palacios, S., Guillen-Grima, F. & Galofre, J. C. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J. Clin. Endocrinol. Metab.* **99**, 923–931 (2014).
27. Hollowell, J. G. et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab.* **87**, 489–499 (2002).
28. Tunbridge, W. M. et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin. Endocrinol.* **7**, 481–493 (1977).
29. Furszyfer, J., Kurland, L. T., McConahey, W. M. & Elveback, L. R. Graves' disease in Olmsted County, Minnesota, 1935 through 1967. *Mayo Clin. Proc.* **45**, 636–644 (1970).
30. Vanderpump, M. P. et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin. Endocrinol.* **43**, 55–68 (1995).
31. Berglund, J., Ericsson, U. B. & Hallengren, B. Increased incidence of thyrotoxicosis in Malmo during the years 1988–1990 as compared to the years 1970–1974. *J. Intern. Med.* **239**, 57–62 (1996).
32. Nystrom, H. F., Jansson, S. & Berg, G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003–2005. *Clin. Endocrinol.* **78**, 768–776 (2013).

33. Knudsen, N. et al. Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. *Eur. J. Endocrinol.* **143**, 485–491 (2000).
34. Bjoro, T. et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). *Eur. J. Endocrinol.* **143**, 639–647 (2000).
35. Konno, N. et al. Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations. *Clin. Endocrinol.* **38**, 273–281 (1993).
36. Walsh, J. P. Managing thyroid disease in general practice. *Med. J. Aust.* **205**, 179–184 (2016).
37. Gopinath, B. et al. Five-year incidence and progression of thyroid dysfunction in an older population. *Intern. Med. J.* **40**, 642–649 (2010).
38. Laurberg, P., Pedersen, K. M., Vestergaard, H. & Sigurdsson, G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area versus high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *J. Intern. Med.* **229**, 415–420 (1991).
39. Laurberg, P. et al. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur. J. Endocrinol.* **155**, 219–228 (2006).
40. Aghini-Lombardi, F. et al. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J. Clin. Endocrinol. Metab.* **84**, 561–566 (1999).
41. Du, Y. et al. Iodine deficiency and excess coexist in china and induce thyroid dysfunction and disease: a cross-sectional study. *PLOS ONE* **9**, e111937 (2014).
42. Tan, L. et al. Prevalence of thyroid dysfunction with adequate and excessive iodine intake in Hebei Province, People's Republic of China. *Public Health Nutr.* **18**, 1692–1697 (2015).
43. Okosieme, O. E. Impact of iodination on thyroid pathology in Africa. *J. R. Soc. Med.* **99**, 396–401 (2006).
44. Ogbera, A. O. & Kuku, S. F. Epidemiology of thyroid diseases in Africa. *Indian J. Endocrinol. Metabolism* **15**, S82–S88 (2011).
45. Muller, G. M., Levitt, N. S. & Louw, S. J. Thyroid dysfunction in the elderly. *South Afr. Med. J.* **87**, 1119–1123 (1997).
46. Kalk, W. J. Thyrotoxicosis in urban black Africans: a rising incidence. *East Afr. Med. J.* **58**, 109–116 (1981).
47. Sarfo-Kantanka, O., Sarfo, F. S., Ansah, E. O. & Kyei, I. Spectrum of Endocrine Disorders in Central Ghana. *Int. J. Endocrinol.* **2017**, 7 (2017).
48. Sarfo-Kantanka, O., Kyei, I., Sarfo, F. S. & Ansah, E. O. Thyroid Disorders in Central Ghana: The Influence of 20 Years of Iodization. *J. Thyroid Res.* **2017**, 8 (2017).
49. Biondi, B. & Kahaly, G. J. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nature reviews. *Endocrinology* **6**, 431–443 (2010).
50. Ogbera, A. O., Fasanmade, O. & Adediran, O. Pattern of thyroid disorders in the southwestern region of Nigeria. *Ethn. Dis.* **17**, 327–330 (2007).
51. Tellez, M., Cooper, J. & Edmonds, C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clin. Endocrinol.* **36**, 291–294 (1992).
52. Okinaka, S. et al. The association of periodic paralysis and hyperthyroidism in Japan. *J. Clin. Endocrinol. Metab.* **17**, 1454–1459 (1957).
53. Kelley, D. E., Gharib, H., Kennedy, F. P., Duda, R. J. Jr & McManis, P. G. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. *Arch. Intern. Med.* **149**, 2597–2600 (1989).
54. Tamai, H. et al. HLA and thyrotoxic periodic paralysis in Japanese patients. *J. Clin. Endocrinol. Metab.* **64**, 1075–1078 (1987).
55. Bartalena, L. & Fatourechi, V. Extrathyroidal manifestations of Graves' disease: a 2014 update. *J. Endocrinol. Invest.* **37**, 691–700 (2014).
56. Bartalena, L. et al. The phenotype of newly diagnosed Graves' disease in Italy in recent years is milder than in the past: results of a large observational longitudinal study. *J. Endocrinol. Invest.* **39**, 1445–1451 (2016).
57. Perros, P. et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. *Br. J. Ophthalmol.* **99**, 1531–1535 (2015).
58. Vitti, P., Rago, T., Tonacchera, M. & Pinchera, A. Toxic multinodular goiter in the elderly. *J. Endocrinol. Invest.* **25**, 16–18 (2002).
59. Pearce, E. N., Farwell, A. P. & Braverman, L. E. Thyroiditis. *N. Engl. J. Med.* **348**, 2646–2655 (2003).
60. Nikolai, T. F., Brosseau, J., Kettrick, M. A., Roberts, R. & Beltaos, E. Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (silent thyroiditis). *Arch. Intern. Med.* **140**, 478–482 (1980).
61. Ross, D. S. Syndromes of thyrotoxicosis with low radioactive iodine uptake. *Endocrinol. Metab. Clin. North Am.* **27**, 169–185 (1998).
62. Alexander, E. K. et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* **27**, 315–389 (2017).
63. Fatourechi, V., Aniszewski, J. P., Fatourechi, G. Z., Atkinson, E. J. & Jacobsen, S. J. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. *J. Clin. Endocrinol. Metab.* **88**, 2100–2105 (2003).
64. Schwartz, F., Bergmann, N., Zerahn, B. & Faber, J. Incidence rate of symptomatic painless thyroiditis presenting with thyrotoxicosis in Denmark as evaluated by consecutive thyroid scintigraphies. *Scand. J. Clin. Lab. Invest.* **73**, 240–244 (2013).
65. Vitug, A. C. & Goldman, J. M. Silent (painless) thyroiditis. Evidence of a geographic variation in frequency. *Arch. Intern. Med.* **145**, 473–475 (1985).
66. Schneeberg, N. G. Silent thyroiditis. *Arch. Intern. Med.* **143**, 2214 (1983).
67. Martino, E., Bartalena, L., Bogazzi, F. & Braverman, L. E. The effects of amiodarone on the thyroid. *Endocr. Rev.* **22**, 240–254 (2001).
68. Bogazzi, F., Tomisti, L., Bartalena, L., Aghini-Lombardi, F. & Martino, E. Amiodarone and the thyroid: a 2012 update. *J. Endocrinol. Invest.* **35**, 340–348 (2012).
69. Zosin, I. & Balas, M. Amiodarone-induced thyroid dysfunction in an iodine-replete area: epidemiological and clinical data. *Endokrynol. Polska* **63**, 2–9 (2012).
70. Tsang, W. & Houlden, R. L. Amiodarone-induced thyrotoxicosis: a review. *Can. J. Cardiol.* **25**, 421–424 (2009).
71. Uchida, T. et al. Prevalence of amiodarone-induced thyrotoxicosis and associated risk factors in Japanese patients. *Int. J. Endocrinol.* **2014**, 534904 (2014).
72. Cukier, P., Santini, F. C., Scaranti, M. & Hoff, A. O. Endocrine side effects of cancer immunotherapy. *Endocr. Relat. Cancer* **24**, T331–T347 (2017).
73. Barroso-Sousa, R. et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol.* **4**, 173–182 (2018).
74. Daniels, G. H. et al. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiple sclerosis. *J. Clin. Endocrinol. Metab.* **99**, 80–89 (2014).
75. Carle, A., Andersen, S. L., Boelaert, K. & Laurberg, P. Management of endocrine disease: subclinical thyrotoxicosis: prevalence, causes and choice of therapy. *Eur. J. Endocrinol.* **176**, R325–R337 (2017).
76. Vadiveloo, T., Donnan, P. T., Cochrane, L. & Leese, G. P. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J. Clin. Endocrinol. Metab.* **96**, E1–E8 (2011).
77. Das, G. et al. Serum thyrotrophin at baseline predicts the natural course of subclinical hyperthyroidism. *Clin. Endocrinol.* **77**, 146–151 (2012).
78. Rosario, P. W. Natural history of subclinical hyperthyroidism in elderly patients with TSH between 0.1 and 0.4 mIU/l: a prospective study. *Clin. Endocrinol.* **72**, 685–688 (2010).
79. Stanbury, J. B. et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* **8**, 83–100 (1998).
80. Roti, E. & Uberti, E. D. Iodine excess and hyperthyroidism. *Thyroid* **11**, 493–500 (2001).
81. Lee, S. Y. et al. A review: Radiographic iodinated contrast media-induced thyroid dysfunction. *J. Clin. Endocrinol. Metab.* **100**, 376–383 (2015).
82. Cooper, D. S. & Laurberg, P. Hyperthyroidism in pregnancy. *Lancet Diabetes Endocrinol.* **1**, 238–249 (2013).
83. Korevaar, T. I. M., Medici, M., Visser, T. J. & Peeters, R. P. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nat. Rev. Endocrinol.* **13**, 610–622 (2017).
84. Korelitz, J. J. et al. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid* **23**, 758–765 (2013).
85. Andersen, S. L., Olsen, J., Carle, A. & Laurberg, P. Hyperthyroidism incidence fluctuates widely in and around pregnancy and is at variance with some other autoimmune diseases: a Danish population-based study. *J. Clin. Endocrinol. Metab.* **100**, 1164–1171 (2015).
86. Okosieme, O. E. & Lazarus, J. H. Important considerations in the management of Graves' disease in pregnant women. *Expert Rev. Clin. Immunol.* **11**, 947–957 (2015).
87. Taylor, P. N. & Vaidya, B. Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. *Eur. Thyroid J.* **1**, 176–185 (2012).
88. Vaidya, B., Williams, G. R., Abraham, P. & Pearce, S. H. Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists. *Clin. Endocrinol.* **68**, 814–820 (2008).
89. Agboola-Abu, C. F. & Kuku, S. F. Experience in the use of radioactive iodine therapy for hyperthyroidism in Nigerian patients. A study of twenty-two patients. *West Afr. J. Med.* **22**, 324–328 (2003).
90. Bath, S. C., Steer, C. D., Golding, J., Emmett, P. & Rayman, M. P. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* **382**, 331–337 (2013).
91. Taylor, P. N., Okosieme, O. E., Dayan, C. M. & Lazarus, J. H. Therapy of endocrine disease: Impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur. J. Endocrinol.* **170**, R1–R15 (2014).
92. Vanderpump, M. P. et al. Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* **377**, 2007–2012 (2011).
93. Bath, S., Walter, A., Taylor, A. & Rayman, M. Iodine status of UK women of childbearing age. *J. Hum. Nutr. Dietet.* **21**, 379–380 (2008).
94. Pearce, E. N. et al. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. *J. Clin. Endocrinol. Metab.* **95**, 3207–3215 (2010).
95. Lazarus, J. H. & Smyth, P. P. Iodine deficiency in the UK and Ireland. *Lancet* **372**, 888 (2008).
96. Delange, F. Iodine deficiency in Europe anno 2002. *Thyroid Int.* **5**, 3–18 (2002).
97. Mazzarella, C. et al. Iodine status assessment in Campania (Italy) as determined by urinary iodine excretion. *Nutrition* **25**, 926–929 (2009).
98. Vitti, P., Delange, F., Pinchera, A., Zimmermann, M. & Dunn, J. T. Europe is iodine deficient. *Lancet* **361**, 1226 (2003).
99. Pearce, E. N., Andersson, M. & Zimmermann, M. B. Global iodine nutrition: where do we stand in 2013? *Thyroid* **23**, 523–528 (2013).
100. Parle, J. V., Franklyn, J. A., Cross, K. W., Jones, S. C. & Sheppard, M. C. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin. Endocrinol.* **34**, 77–83 (1991).
101. Gussekloo, J. et al. Thyroid status, disability and cognitive function, and survival in old age. *JAMA* **292**, 2591–2599 (2004).
102. Asvold, B. O., Vatten, L. J. & Bjoro, T. Changes in the prevalence of hypothyroidism: the HUNT Study in Norway. *Eur. J. Endocrinol.* **169**, 613–620 (2013).
103. McGrogan, A., Seaman, H. E., Wright, J. W. & de Vries, C. S. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clin. Endocrinol.* **69**, 687–696 (2008).
104. Canaris, G. J., Manowitz, N. R., Mayor, G. & Ridgway, E. C. The Colorado thyroid disease prevalence study. *Arch. Intern. Med.* **160**, 526–534 (2000).
105. Flynn, R. W., MacDonald, T. M., Morris, A. D., Jung, R. T. & Leese, G. P. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. *J. Clin. Endocrinol. Metab.* **89**, 3879–3884 (2004).
106. Valdes, S. et al. Population-based national prevalence of thyroid dysfunction in Spain and associated factors: Di@bet.es study. *Thyroid* **27**, 156–166 (2017).
107. Sgarbi, J. A., Matsumura, L. K., Kasamatsu, T. S., Ferreira, S. R. & Maciel, R. M. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur. J. Endocrinol.* **162**, 569–577 (2010).

108. Kasagi, K. et al. Thyroid function in Japanese adults as assessed by a general health checkup system in relation with thyroid-related antibodies and other clinical parameters. *Thyroid* **19**, 937–944 (2009).
109. Al Shahrani, A. S. et al. The epidemiology of thyroid diseases in the Arab world: a systematic review. *J. Public Health Epidemiol.* **8**, 17–26 (2016).
110. Amouzegar, A. et al. Natural course of euthyroidism and clues for early diagnosis of thyroid dysfunction: Tehran Thyroid Study. *Thyroid* **27**, 616–625 (2017).
111. Amouzegar, A. et al. The prevalence, incidence and natural course of positive antithyroperoxidase antibodies in a population-based study: Tehran Thyroid Study. *PLOS ONE* **12**, e0169283 (2017).
112. Knudsen, N., Jorgensen, T., Rasmussen, S., Christiansen, E. & Perrild, H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin. Endocrinol.* **51**, 361–367 (1999).
113. Okosieme, O. E., Taylor, R. C., Ohwovoriole, A. E., Parkes, A. B. & Lazarus, J. H. Prevalence of thyroid antibodies in Nigerian patients. *QJM* **100**, 107–112 (2007).
114. Satti, H. et al. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. *Int. J. Tuberculosis Lung Dis.* **16**, 468–472 (2012).
115. Munivenkatappa, S. et al. Drug-induced hypothyroidism during anti-tuberculosis treatment of multidrug-resistant tuberculosis: notes from the field. *J. Tuberculosis Res.* **4**, 105–110 (2016).
116. Shan, Z. et al. Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. *Thyroid* **26**, 1125–1130 (2016).
117. Teng, W. et al. Effect of iodine intake on thyroid diseases in China. *N. Engl. J. Med.* **354**, 2783–2793 (2006).
118. Unnikrishnan, A. G. et al. Prevalence of hypothyroidism in adults: an epidemiological study in eight cities of India. *Indian J. Endocrinol. Metab.* **17**, 647–652 (2013).
119. Bagcchi, S. Hypothyroidism in India: more to be done. *Lancet Diabetes Endocrinol.* **2**, 778 (2014).
120. Medici, M., Korevaar, T. I., Visser, W. E., Visser, T. J. & Peeters, R. P. Thyroid function in pregnancy: what is normal? *Clin. Chem.* **61**, 704–713 (2015).
121. Taylor, P. N., Okosieme, O. E., Premawardhana, L. & Lazarus, J. H. Should all women be screened for thyroid dysfunction in pregnancy? *Womens Health* **11**, 295–307 (2015).
122. Krassas, G. E., Poppe, K. & Glinoer, D. Thyroid function and human reproductive health. *Endocr. Rev.* **31**, 702–755 (2010).
123. Stagnaro-Green, A. et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* **21**, 1081–1125 (2011).
124. Zhang, Y., Wang, H., Pan, X., Teng, W. & Shan, Z. Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: a systematic review and meta-analysis. *PLOS ONE* **12**, e0175708 (2017).
125. Korevaar, T. I. et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. *J. Clin. Endocrinol. Metab.* **98**, 4382–4390 (2013).
126. Lazarus, J. H. et al. Antenatal thyroid screening and childhood cognitive function. *N. Engl. J. Med.* **366**, 493–501 (2012).
127. Casey, B. M. et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N. Engl. J. Med.* **376**, 815–825 (2017).
128. Dosiou, C. et al. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J. Clin. Endocrinol. Metab.* **97**, 1536–1546 (2012).
129. Gruters, A. & Krude, H. Update on the management of congenital hypothyroidism. *Horm. Res.* **68** (Suppl. 5), 107–111 (2007).
130. Fisher, D. A. Second International Conference on Neonatal Thyroid Screening: progress report. *J. Pediatr.* **102**, 653–654 (1983).
131. Albert, B. B. et al. Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993–2010. *J. Clin. Endocrinol. Metab.* **97**, 3155–3160 (2012).
132. Deladoey, J., Ruel, J., Giguere, Y. & Van Vliet, G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Quebec. *J. Clin. Endocrinol. Metab.* **96**, 2422–2429 (2011).
133. Ford, G. & LaFranchi, S. H. Screening for congenital hypothyroidism: a worldwide view of strategies. *Best Pract. Res. Clin. Endocrinol. Metab.* **28**, 175–187 (2014).
134. Gittoes, N. J. L. & Franklyn, J. A. Drug-induced thyroid disorders. *Drug Safety* **13**, 46–55 (1995).
135. Martino, E. et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann. Intern. Med.* **101**, 28–34 (1984).
136. Mahzari, M., Arnaout, A. & Freedman, M. S. Alemtuzumab induced thyroid disease in multiple sclerosis: a review and approach to management. *Can. J. Neurol. Sci.* **42**, 284–291 (2015).
137. Wolter, P. et al. The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *Br. J. Cancer* **99**, 448–454 (2008).
138. Markou, K., Georgopoulos, N., Kyriazopoulou, V. & Vagenakis, A. G. Iodine-Induced hypothyroidism. *Thyroid* **11**, 501–510 (2001).
139. Leung, A. M. et al. Potential risks of excess iodine ingestion and exposure: statement by the american thyroid association public health committee. *Thyroid* **25**, 145–146 (2015).
140. IGN. Iodine Global Network Annual Report 2016. *IGN* http://www.ign.org/ (2016).
141. Dasgupta, P. K., Liu, Y. & Dyke, J. V. Iodine nutrition: iodine content of iodized salt in the United States. *Environ. Sci. Technol.* **42**, 1315–1323 (2008).
142. Premawardhana, L. D. et al. Increased prevalence of thyroglobulin antibodies in Sri Lankan schoolgirls — is iodine the cause? *Eur. J. Endocrinol.* **143**, 185–188 (2000).
143. Sundick, R. S., Bagchi, N. & Brown, T. R. The role of iodine in thyroid autoimmunity: from chickens to humans: a review. *Autoimmunity* **13**, 61–68 (1992).
144. Okosieme, O. E. et al. Thyroglobulin epitope recognition in a post iodine-supplemented Sri Lankan population. *Clin. Endocrinol.* **59**, 190–197 (2003).
145. Bulow Pedersen, I. et al. A cautious iodization program bringing iodine intake to a low recommended level is associated with an increase in the prevalence of thyroid autoantibodies in the population. *Clin. Endocrinol.* **75**, 120–126 (2011).
146. Pedersen, I. B. et al. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J. Clin. Endocrinol. Metab.* **92**, 3122–3127 (2007).
147. Buziak-Bereza, M., Golkowski, F. & Szybinski, Z. Disturbances of thyroid function in adult population of the city of Cracow followed up for ten years observation [Polish]. *Przegl. Lek.* **62**, 676–679 (2005).
148. Laurberg, P. et al. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *J. Clin. Endocrinol. Metab.* **83**, 765–769 (1998).
149. Konno, N., Makita, H., Yuri, K., Iizuka, N. & Kawasaki, K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *J. Clin. Endocrinol. Metab.* **78**, 393–397 (1994).
150. Hong, A., Stokes, B., Otahal, P., Owens, D. & Burgess, J. R. Temporal trends in thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (ATPO) testing across two phases of iodine fortification in Tasmania (1995–2013). *Clin. Endocrinol.* **87**, 386–393 (2017).
151. Parveen, S., Latif, S. A., Kamal, M. M. & Uddin, M. M. Effects of long term iodized table salt consumption on serum T3, T4 and TSH in an iodine deficient area of Bangladesh. *Mymensingh Med. J.* **16**, 57–60 (2007).
152. Tammaro, A., Pigliacelli, F., Fumarola, A. & Persechino, S. Trends of thyroid function and autoimmunity to 5 years after the introduction of mandatory iodization in Italy. *Eur. Ann. Allergy Clin. Immunol.* **48**, 77–81 (2016).
153. Bourdoux, P. P., Ermans, A. M., Mukalay wa Mukalay, A., Filetti, S. & Vigneri, R. Iodine-induced thyrotoxicosis in Kivu, Zaire. *Lancet* **347**, 552–553 (1996).
154. Todd, C. H. et al. Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe. *Lancet* **346**, 1563–1564 (1995).
155. Connolly, R. J. An increase in thyrotoxicosis in southern Tasmania after an increase in dietary iodine. *Med. J. Aust.* **1**, 1268–1271 (1971).
156. Elnagar, B. et al. The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid-related hormones. *J. Clin. Endocrinol. Metab.* **80**, 891–897 (1995).
157. Okosieme, O. E. Iodisation in displaced African populations. *Lancet* **373**, 214 (2009).
158. Aakre, I. et al. Development of thyroid dysfunction among women with excessive iodine intake — a 3-year follow-up. *J. Trace Elem. Med. Biol.* **31**, 61–66 (2015).
159. Marwaha, R. K. et al. Reference range of thyroid hormones in healthy school-age children: country-wide data from India. *Clin. Biochem.* **43**, 51–56 (2010).
160. Taylor, P. N. et al. Whole-genome sequence-based analysis of thyroid function. *Nat. Commun.* **6,** 5681 (2015).
161. Kus, A. et al. The association of thyroid peroxidase antibody risk loci with susceptibility to and phenotype of Graves' disease. *Clin. Endocrinol.* **83**, 556–562 (2015).
162. Meyerovitch, J. et al. Serum thyrotropin measurements in the community. Five-year follow-up in a large network of primary care physicians. *Arch. Intern. Med.* **167**, 1533–1538 (2007).
163. Stott, D. J. et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N. Engl. J. Med.* **376**, 2534–2544 (2017).
164. Collet, T. H. et al. Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. *J. Clin. Endocrinol. Metab.* **99**, 3353–3362 (2014).
165. Cooper, D. S. & Biondi, B. Subclinical thyroid disease. *Lancet* **379**, 1142–1154 (2012).
166. Taylor, P. N., Razvi, S., Pearce, S. H. & Dayan, C. M. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J. Clin. Endocrinol. Metab.* **98**, 3562–3571 (2013).
167. Rieben, C. et al. Subclinical thyroid dysfunction and the risk of cognitive decline: a meta-analysis of prospective cohort studies. *J. Clin. Endocrinol. Metab.* **101**, 4945–4954 (2016).
168. Eligar, V., Taylor, P., Okosieme, O., Leese, G. & Dayan, C. Thyroxine replacement: a clinical endocrinologist's viewpoint. *Ann. Clin. Biochem.* **53**, 421–433 (2016).
169. IGN Iodine Global Network. *IGN* http://www.ign.org/ (2018).
170. Vanderpump, M. in *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text* (ed. Utiger, R. D. & Braverman, L. E.) 398–496 (JB Lippincott-Raven, 2005).
171. Schultheiss, U. T. et al. A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. *J. Clin. Endocrinol. Metab.* **100**, E799–E807 (2015).
172. Marinò, M., Latrofa, F., Menconi, F., Chiovato, L. & Vitti, P. Role of genetic and non-genetic factors in the etiology of Graves' disease. *J. Endocrinol. Invest.* **38**, 283–294 (2015).
173. Prummel, M. F. & Wiersinga, W. M. Smoking and risk of Graves' disease. *JAMA* **269**, 479–482 (1993).
174. Nyirenda, M. J., Taylor, P. N., Stoddart, M., Beckett, G. J. & Toft, A. D. Thyroid-stimulating hormone-receptor antibody and thyroid hormone concentrations in smokers versus nonsmokers with Graves disease treated with carbimazole. *JAMA* **301**, 162–164 (2009).
175. Strieder, T. G., Prummel, M. F., Tijssen, J. G., Endert, E. & Wiersinga, W. M. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. *Clin. Endocrinol.* **59**, 396–401 (2003).
176. Belin, R. M., Astor, B. C., Powe, N. R. & Ladenson, P. W. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab.* **89**, 6077–6086 (2004).
177. Asvold, B. O., Bjoro, T., Nilsen, T. I. & Vatten, L. J. Tobacco smoking and thyroid function: a population-based study. *Arch. Intern. Med.* **167**, 1428–1432 (2007).
178. Carlé, A. et al. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case–control study. *Eur. J. Endocrinol.* **167**, 483–490 (2012).
179. Tomer, Y. & Davies, T. F. Infection, thyroid disease, and autoimmunity. *Endocr. Rev.* **14**, 107–120 (1993).
180. Mogensen, E. F. & Green, A. The epidemiology of thyrotoxicosis in Denmark. Incidence and geographical variation in the Funen region 1972–1974. *Acta Med. Scand.* **208**, 183–186 (1980).
181. Berglund, J., Christensen, S. B. & Hallengren, B. Total and age-specific incidence of Graves' thyrotoxicosis, toxic nodular goitre and solitary toxic adenoma in Malmo 1970–1974. *J. Intern. Med.* **227**, 137–141 (1990).

182. Galofre, J. C. et al. Incidence of different forms of thyroid dysfunction and its degrees in an iodine sufficient area. *Thyroidology* **6**, 49–54 (1994).
183. Volzke, H. et al. The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. *Thyroid* **13**, 803–810 (2003).
184. O'Leary, P. C. et al. Investigations of thyroid hormones and antibodies based on a community health survey: the Busselton thyroid study. *Clin. Endocrinol.* **64**, 97–104 (2006).
185. Leese, G. P. et al. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS). *Clin. Endocrinol.* **68**, 311–316 (2008).
186. Lucas, A. et al. Undiagnosed thyroid dysfunction, thyroid antibodies, and iodine excretion in a Mediterranean population. *Endocr* **38**, 391–396 (2010).
187. Delshad, H., Mehran, L., Tohidi, M., Assadi, M. & Azizi, F. The incidence of thyroid function abnormalities & natural course of subclinical thyroid disorders, Tehran, I. R. Iran. *J. Endocrinol. Invest.* **35**, 516–521 (2012).
188. Sriphrapradang, C. et al. Reference ranges of serum TSH, FT4 and thyroid autoantibodies in the Thai population: the national health examination survey. *Clin. Endocrinol.* **80**, 751–756 (2014).
189. Hoogendoorn, E. H. et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clin. Chem.* **52**, 104–111 (2006).
190. Marwaha, R. K. et al. The evolution of thyroid function with puberty. *Clin. Endocrinol.* **76**, 899–904 (2012).
191. Laurberg, P., Bulow Pedersen, I., Pedersen, K. M. & Vestergaard, H. Low incidence rate of overt hypothyroidism compared with hyperthyroidism in an area with moderately low iodine intake. *Thyroid* **9**, 33–38 (1999).
192. Galofre, J. C., Fernandez-Calvet, L., Rios, M. & Garcia-Mayor, R. V. Increased incidence of thyrotoxicosis after iodine supplementation in an iodine sufficient area. *J. Endocrinol. Invest.* **17**, 23–27 (1994).
193. Yang, F. et al. Epidemiological survey on the relationship between different iodine intakes and the prevalence of hyperthyroidism. *Eur. J. Endocrinol.* **146**, 613–618 (2002).
194. Golkowski, F. et al. Increased prevalence of hyperthyroidism as an early and transient side-effect of implementing iodine prophylaxis. *Public Health Nutr.* **10**, 799–802 (2007).
195. Heydarian, P., Ordookhani, A. & Azizi, F. Goiter rate, serum thyrotropin, thyroid autoantibodies and urinary iodine concentration in Tehranian adults before and after national salt iodization. *J. Endocrinol. Invest.* **30**, 404–410 (2007).
196. Cerqueira, C. et al. Doubling in the use of thyroid hormone replacement therapy in Denmark: association to iodization of salt? *Eur. J. Epidemiol.* **26**, 629–635 (2011).
197. Aghini Lombardi, F. et al. The effect of voluntary iodine prophylaxis in a small rural community: the Pescopagano survey 15 years later. *J. Clin. Endocrinol. Metab.* **98**, 1031–1039 (2013).

Author contributions

P.N.T., D.A., A.S., G.G. and O.E.O. researched data for the article, made substantial contributions to discussion of content, wrote the article and reviewed and/or edited the manuscript before submission. C.M.D. and J.H.L. made substantial contributions to discussion of content and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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