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Thyroid hormone sensitivity and cardiovascular disease in the euthyroid population: indices, mechanisms, and translational gaps

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Thyroid hormones regulate cardiac contractility, electrophysiology, vascular tone, and lipid metabolism. Beyond overt thyroid disease, altered tissue sensitivity to thyroid hormone can be quantified in people with normal circulating hormone levels using central indices (TFQI, PTFQI, TSHI, TT4RI) derived from free thyroxine and TSH, and a peripheral index (the FT3/FT4 ratio). This review summarizes what these indices can and cannot tell us about cardiovascular risk. Most of the evidence is cross-sectional and comes from a small number of cohorts. Reduced sensitivity tracks most consistently with atherogenic dyslipidemia, whereas associations with arrhythmia, atherosclerosis, hypertension, and heart failure vary in direction and strength. The central indices, however, largely capture variation in the hypothalamic-pituitary-thyroid set point rather than tissue sensitivity, and none has been validated against a physiological reference standard. Single measurements add further uncertainty through substantial within-person variation. Two translational problems remain: the risk markers and the available TRβ-selective drugs act on different physiological axes, and almost no study has tested whether adding an index improves established risk models. Before these indices can inform clinical decisions, their repeatability and construct validity must be established, causality tested in prospective and genetic designs, and incremental predictive value demonstrated.

KEYWORDS
cardiovascular disease, lipid metabolism, thyroid hormone receptors, thyroid hormone sensitivity, thyroid hormones

1 Introduction

Thyroid hormones are established regulators of cardiovascular physiology, acting through genomic and non-genomic pathways to set cardiac contractility, heart rate, vascular tone, and lipid turnover (1, 2). Clinical attention has long centered on overt hyperthyroidism and hypothyroidism. A less familiar question is whether two people with identical, normal thyroid test results can still differ in how their tissues respond to thyroid hormone, and whether that difference carries cardiovascular meaning.

The phenomenon was first described as a rare syndrome. In 1967, Refetoff and colleagues reported siblings who were deaf and goitrous and had high circulating hormone levels without the expected suppression of TSH (3). A molecular explanation followed in 1989 with the discovery of thyroid hormone receptor beta gene defects (4), and receptor alpha defects were added later (5). What began as a single-gene diagnosis has since widened into a broader framework of impaired sensitivity that includes milder variation across the general euthyroid population (6, 7). To study that variation at scale, investigators built quantitative indices from routine thyroid tests, opening a productive but still immature line of epidemiological research (8).

Most existing reviews have catalogued the associations without asking whether the indices themselves are valid surrogates for tissue sensitivity, or what stands between those observations and clinical practice. Two gaps are rarely discussed. One is structural: the risk markers locate the pituitary set point, whereas the thyroid mimetics in clinical use act mainly on the liver. The other is measurement error introduced by cardiology-specific exposures such as iodinated contrast, amiodarone, and acute illness, which shift the index without changing the underlying sensitivity. This review examines five cardiovascular domains with those gaps in view, evaluates the construct validity and temporal repeatability of the indices, and sets out what it would take to move from association to causal evidence and clinical use.

For this narrative review, we searched PubMed and Web of Science from inception through June 2026, combining index terms (thyroid hormone sensitivity, thyroid hormone resistance, impaired sensitivity to thyroid hormone, TFQI, PTFQI, TSH index, thyrotroph T4 resistance index, FT3/FT4 ratio) with cardiovascular terms (cardiovascular disease, atherosclerosis, hypertension, dyslipidemia, atrial fibrillation, heart failure). We included original observational studies, Mendelian randomization analyses, randomized controlled trials, and key reviews in English on human populations, and excluded conference abstracts, non-English publications, single case reports, and purely *in vitro* or animal studies. Reference lists of included articles were manually screened, and background reference material on thyroid biology, receptor genetics, drug trials, and statistical methods - together with a few historical or mechanistic reports - was drawn from these lists and the initial searches rather than as formal search hits. No systematic review protocol was registered and no quantitative risk-of-bias assessment was performed, reflecting the narrative scope of the review.

2 Thyroid hormone metabolism and sensitivity indices

2.1 Metabolism and regulation of thyroid hormones

Thyroid hormones govern whole-body energy expenditure and the metabolism of proteins, carbohydrates, lipids, and vitamins. Their production is controlled by the hypothalamic-pituitary-thyroid (HPT) axis. The hypothalamus releases thyrotropin-releasing hormone, which stimulates pituitary thyrotrophs to secrete thyroid-stimulating hormone (TSH); TSH then drives thyroid follicular cell growth and hormone synthesis (1). Circulating hormone, predominantly thyroxine (T4), feeds back negatively on both the hypothalamus and pituitary, so that small changes in T4 produce amplified changes in TSH. This is why serum TSH is the most sensitive routine marker of thyroid status, although, as discussed below, it is not a direct readout of tissue response.

The thyroid secretes mainly T4 and a smaller amount of triiodothyronine (T3) (9). T4 acts largely as a prohormone and has a long half-life, whereas T3 is the principal active form with a much shorter half-life and roughly tenfold higher affinity for nuclear receptors (10, 11). Deiodinase enzymes convert T4 to T3 in peripheral tissues, making this conversion a decisive step in determining how much active hormone reaches a given organ.

In blood, more than 99 percent of T4 and T3 is bound to thyroxine-binding globulin, transthyretin, and albumin. Only the unbound free fractions (FT4 and FT3) enter cells through specific transporters. Once inside, T3 binds the receptor isoforms TRα and TRβ and modulates gene transcription. The two isoforms have distinct tissue distributions, a point that matters for both cardiovascular biology and the side-effect profile of thyroid-mimetic drugs.

2.2 Thyroid hormone sensitivity and related indices

Resistance to thyroid hormone (RTH) is defined by reduced target-tissue responsiveness, classically presenting as elevated FT4 with non-suppressed TSH (3, 12). The 1989 discovery of THRB gene defects, followed by THRA defects, established the inherited forms RTHβ and RTHα (4, 5). To cover alterations beyond receptor defects, the umbrella term impaired sensitivity to thyroid hormone has been proposed (6). It includes the syndrome of inappropriate TSH secretion in which no THRA or THRB defect is found, sometimes called nonTR-RTH (7, 13), as well as milder, apparently acquired shifts in the HPT set point that produce the same pattern of high FT4 with normal or high TSH.

Several indices quantify these states, and they fall into two groups. The central indices reflect pituitary feedback sensitivity and include the thyroid feedback quantile-based index (TFQI) (8), its parametric version (PTFQI) (14), the TSH index (TSHI) (15), and the thyrotroph T4 resistance index (TT4RI) (16). The most common peripheral index is the FT3/FT4 ratio, which is interpreted as a measure of peripheral T4-to-T3 conversion, tissue sensitivity, or both. These indices are convenient, but convenience should not be mistaken for validation. Three limitations deserve emphasis before the disease evidence is considered.

First, the four central indices are not independent measurements. They are all computed from the same two analytes, FT4 and TSH, using different transformations, and they are therefore highly correlated. When several of them show the same association in one dataset, that is one finding expressed four ways rather than four converging lines of evidence. The literature often reports them separately, which can overstate the amount of supporting evidence.

Second, a central index measures the position of the HPT set point more directly than it measures the sensitivity of peripheral tissues. Pituitary feedback and the response of myocardium, liver, or vascular endothelium need not move together, as the variable cardiac phenotype of RTH demonstrates. The FT3/FT4 ratio is likewise influenced by carrier proteins, deiodinase activity, acute illness, renal and hepatic function, and nutritional state. To our knowledge, none of these indices has been tested against a physiological reference standard, such as the tissue response to administered thyroid hormone, so the claim that they quantify tissue sensitivity remains an assumption rather than a validated measurement.

Third, the indices rely on a single blood draw, yet thyroid tests show appreciable within-person variation. In healthy adults sampled repeatedly, indices of individuality were low, about 0.49 for TSH, 0.54 to 0.58 for T3, and 0.59 to 0.60 for FT4 (17, 18). Values this low mean that population reference ranges are insensitive to changes that matter for a given individual and that a set point estimated from one measurement carries real uncertainty. Whether the derived indices are stable enough over time to serve as traits, rather than snapshots, has not been established.

These indices are therefore best treated as inexpensive screening markers of set-point variation; the burden of proof lies with investigators to show that they represent tissue sensitivity. That distinction shapes how the disease associations below should be interpreted.

2.3 Associations with cardiovascular disease

Throughout this section, higher central index values and a lower FT3/FT4 ratio are taken to indicate reduced sensitivity. Table 1 summarizes the direction of each association.

2.3.1 Arrhythmia

Thyroid hormone sets sinus node automaticity and the expression of ion channels that govern depolarization and repolarization. Excess hormone produces sinus tachycardia and atrial fibrillation, while hormone deficiency slows the heart. Monogenic RTH offers a natural experiment. Atrial fibrillation or flutter is reported in up to 20 percent of patients with RTHβ despite elevated circulating hormone (19), and cardiac involvement, including tachycardia and impaired exercise tolerance, is common in this group (20). These observations show that the cardiac response cannot be inferred from circulating levels alone.

Population studies reach mixed conclusions. In patients with coronary heart disease, TFQI was inversely associated with atrial fibrillation (odds ratio 0.783, 95%CI 0.735 - 0.836), with a stronger association in women and older adults (21). A small Spanish cohort reported a markedly raised odds of atrial fibrillation at reduced sensitivity (odds ratio 8.13), but the confidence interval was extremely wide (1.33 to 158.20) and the trend was borderline, so this is best read as an imprecise exploratory estimate rather than a stable effect size (14). At the other end of the rate spectrum, higher central indices and a lower FT3/FT4 ratio were associated with bradycardia, defined as a heart rate no higher than 60 beats per minute (22).

These findings are less contradictory than they first appear. A high central index marks pituitary resistance, while peripheral cardiac exposure can be high, low, or normal depending on where the defect lies, so both tachyarrhythmia and bradycardia are biologically plausible. What the data do not yet support is a common, quantifiable effect across populations; the estimates are too few and too imprecise.

2.3.2 Atherosclerosis

Thyroid hormone acts on vascular endothelium and smooth muscle, supporting nitric oxide production, vasodilation, and vascular remodeling, so reduced sensitivity could plausibly accelerate atherogenesis (1). In a Chinese cohort, higher central indices and a lower FT3/FT4 ratio were associated with carotid plaque and thicker intima-media, indicating greater atherosclerotic burden at lower sensitivity (odds ratio 1.50, 95%CI 1.26 - 1.78) (23). Studies of patients undergoing coronary angiography linked lower FT3 and a lower FT3/FT4 ratio to more severe coronary disease (24). In the general NHANES population, a higher FT3/FT4 ratio was independently associated with lower all-cause and cardiovascular mortality (25).

Not all cohorts agree. In a large Korean dataset, higher PTFQI, indicating reduced sensitivity, was associated with lower odds of atherosclerotic cardiovascular disease, with a log-odds of minus 0.31 (95%CI −0.53 - −0.08) (26), the opposite direction to the Chinese angiography studies. A Beijing working population also found that the relationship between TFQI and cardiovascular risk factors depended strongly on age and sex (27).

The most likely explanation for the divergence is not simply ethnic difference. Several positive studies conditioned on people who already had coronary disease or who were referred for angiography, whereas the Korean result came from a broader screening population. Analyzing only the diseased group can induce collider bias and reverse an association, quite apart from any genuine biological contrast. Acute illness and the stress of hospitalization also lower FT3. On causality, genetic evidence adds nuance. In over 105,000 individuals, genetically predicted lower TSH was associated with a higher risk of atrial fibrillation, myocardial infarction, and aortic valve stenosis, which supports a causal component for thyroid activity, while no clear effect emerged for stroke or heart failure (28). Because that instrument targets TSH rather than a sensitivity index, it does not directly establish that reduced sensitivity causes atherosclerotic disease. Taken together, the evidence supports a link between lower peripheral hormone exposure and disease severity in sicker patients but does not establish reduced sensitivity as a cause of atherosclerosis in healthy people.

2.3.3 Hypertension

Blood pressure reflects the balance between thyroid-driven vasodilation and sympathetic tone, together with renal sodium handling and the renin-angiotensin system. Thyroid hormone lowers systemic vascular resistance and increases renal blood flow, so altered sensitivity could shift pressure in either direction.

TABLE 1 Reported associations between thyroid hormone sensitivity indices and cardiovascular conditions.

Condition	Index (axis)	Population/study	Year	Direction for reduced sensitivity (effect size)	Design/evidence level
Atrial fibrillation	Central	CHD patients, China (Liu F)	2023	Inverse: lower odds of AF (OR 0.783)	Cross-sectional
Atrial fibrillation	Central	Small Spanish cohort (Alonso-Ventura)	2022	Higher odds (OR 8.13; 95% CI 1.33 - 158.20), very imprecise	Cross-sectional
Bradycardia	Central + FT3/FT4	Euthyroid adults (Ye)	2026	Higher odds of heart rate ≤60 bpm	Cross-sectional
Atrial fibrillation in RTHβ	Genotype (THRB)	RTHβ cohorts (Illouz)	2021	AF/flutter in up to 20%	Case series
Carotid/coronary atherosclerosis	Central, FT3/FT4	Chinese CHD/angiography (Liu Y, Ling)	2022, 2015	Greater plaque and stenosis severity	Cross-sectional
All-cause/CV mortality	FT3/FT4	General population, NHANES (Lang)	2022	Reduced sensitivity (lower FT3/FT4) → higher mortality	Cross-sectional
ASCVD	PTFQI	Korean screening population (Choe)	2025	Inverse: lower ASCVD (log-odds -0.31, 95%CI −0.53 - −0.08)	Cross-sectional
AF, myocardial infarction, aortic valve stenosis	Genetically predicted TSH	105,224 adults, CGPS (Dalila)	2023	Higher risk with genetically lower TSH; no clear effect on stroke or HF	Mendelian randomization
Hypertension	Central	Community/diabetes samples (Gu, Mehran, Lv, Yu)	2018, 2022, 2023, 2024	Higher blood pressure and hypertension prevalence	Cross-sectional
Dyslipidemia	Central, FT3/FT4	Euthyroid adults (Liu Y, Sun, Lv, Shi)	2023, 2022, 2023, 2025	Higher LDL-C, triglycerides, remnant cholesterol	Cross-sectional
Dyslipidemia in RTHβ	Genotype (THRB)	RTHβ (Moran)	2021	Blunted PCSK9 and LDL-C lowering	Case-control
Heart failure (low-T3 state)	FT3	Chronic HF (Lisco)	2020	Low T3 in 15 - 30%, tracks severity	Cross-sectional
Heart failure (T3 therapy)	T3 intervention	RCT and meta-analysis (Pingitore, Shi C)	2008, 2022	Higher LVEF (WMD + 5.61 points), lower BNP/NE; surrogate endpoints	Small RCT/meta-analysis
Incident type 2 diabetes	PTFQI	German SHIP, 5-year follow-up (Laclaustra)	2024	Higher incidence (IRR 1.64 in top group)	Prospective cohort
All-cause mortality	TFQI	Spanish Di@bet.es, 7.3-year follow-up (Alonso)	2021	Higher mortality (RR 2.61, TFQI >95th vs ≤5th percentile)	Prospective cohort
Risk-model increment	PTFQI added to GRACE	Acute coronary syndrome (He)	2025	AUROC 0.646 - 0.759 for MACCE	Retrospective cohort

Reduced sensitivity is defined as higher central index values and a lower FT3/FT4 ratio, as set out in section 2.3. Opposite directions between diseased/angiography samples and screening populations may reflect collider bias and reverse causation. Only one study reported incremental prediction, and prospective cardiovascular endpoint data are lacking.

In community and outpatient samples, higher TFQI and related central indices were associated with higher blood pressure and a greater prevalence of hypertension, including in people with diabetes (29–31). A study that stratified blood pressure by severity reported that the association strengthened at higher grades, suggesting a graded relationship (32). The small Spanish cohort again reported a raised odds of hypertension at reduced sensitivity (odds ratio 3.19, 95%CI 1.14 - 9.94) (14).

These effect sizes are modest and the cohorts differ in how they define and treat hypertension, which matters because antihypertensive drugs themselves alter the indices. Of all the cardiovascular endpoints examined here, blood pressure shows the weakest and least specific signal, and no study has shown that a sensitivity index predicts incident hypertension beyond established determinants. The blood pressure evidence is therefore best regarded as hypothesis-generating.

2.3.4 Dyslipidemia

The lipid signal is the most consistent in this literature and has the clearest mechanistic basis. TRβ is the dominant receptor isoform in liver, where thyroid hormone induces the LDL receptor, suppresses PCSK9 through an SREBP-2-dependent pathway, and promotes cholesterol clearance and bile acid synthesis (33). In euthyroid adults, higher central indices and a lower FT3/FT4 ratio were associated with higher total and LDL cholesterol, triglycerides, and remnant cholesterol, and with a greater prevalence of dyslipidemia (27, 31, 34, 35). The remnant cholesterol association is clinically relevant because it links reduced sensitivity specifically to the triglyceride-rich lipoproteins that drive residual cardiovascular risk (35).

The monogenic form again informs the mechanism. In RTHβ, elevated endogenous hormone did not lower PCSK9 or LDL

cholesterol as expected, and the normal lipid-lowering response was blunted (36). This mirrors the epidemiological direction and suggests that hepatic sensitivity sets the strength of the lipid response.

The lipid evidence is more persuasive than the other endpoints because population association, receptor biology, and the RTH phenotype all point the same way. Even here the effect on clinical lipids is modest in euthyroid people, and the marker (a pituitary set-point index) is not the same measurement as the hepatic pathway it is linked to.

2.3.5 Heart failure

Heart failure deserves separate attention because low thyroid activity is both common in this population and plausibly modifiable. The low-T3 state, characterized by low FT3 with normal FT4 and TSH, is reported in roughly 15 to 30 percent of patients with chronic heart failure and tracks disease severity (37). In myocardium, thyroid hormone promotes the faster alpha isoform of myosin heavy chain, supports SERCA2-mediated calcium reuptake, and increases contractility while reducing systemic vascular resistance. When T3 falls, these adaptations reverse in a direction that favors impaired relaxation and remodeling.

Small intervention studies provide proof of mechanism. In a randomized placebo-controlled trial, short-term T3 infusion in patients with heart failure and low T3 increased stroke volume and lowered heart rate, norepinephrine, NT-proBNP, and aldosterone without provoking ischemia or arrhythmia (38). A meta-analysis of randomized trials of thyroid hormone therapy in heart failure reported improved left ventricular ejection fraction (weighted mean difference 5.61 percentage points, 95% CI 4.38 - 6.85) and lower BNP and norepinephrine (39). Earlier work with the thyroid hormone analog DITPA explored the same approach and found improved cardiac output and lower vascular resistance, though systemic side effects limited development (40).

These data should not, however, be read as evidence that reduced sensitivity causes heart failure. Low T3 in a hospitalized, often malnourished patient is as much a marker of illness severity, inflammation, and catabolism as a driver of disease, and the same applies to a low FT3/FT4 ratio. The mechanistic signal is genuine, and the physiological rationale for replacement is the strongest of any endpoint considered here, but the trials were small, short, and surrogate-based. Before therapy can be recommended, a trial powered for hospitalization and survival is needed, with patients selected by a validated marker rather than a single low T3 value.

3 Discussion

3.1 Strength and hierarchy of the evidence

The evidence base has a clear hierarchy, and most of it sits at the lower levels. The dominant design is cross-sectional, often within a single cohort, with exposure and outcome measured at the same visit. Truly prospective data are sparse and come from independent groups. In the German SHIP cohort, higher PTFQI predicted incident type 2 diabetes over five years, with an incidence rate ratio of 1.64 (95%CI 1.05 - 2.59) in the highest group (41). In the Spanish Di@bet.es community study, the highest TFQI group had a raised risk of all-cause mortality over 7.3 years (relative risk 2.61, 95%CI 1.16 - 5.89) (42). These longitudinal signals are more credible than cross-sectional correlations, yet they concern metabolic incidence and total mortality rather than a specific cardiovascular endpoint, and the mortality estimate rests on relatively few deaths. Genetic evidence is mixed rather than negative: in the same Mendelian randomization analysis, genetically lower TSH raised the risk of atrial fibrillation, myocardial infarction, and aortic valve stenosis but not stroke or heart failure (28). Because the instrument indexes TSH rather than sensitivity, it does not test the central claim directly. Reduced sensitivity is therefore associated with a poorer cardiometabolic profile but has not been shown to cause cardiovascular disease.

3.2 The marker-target mismatch

A structural problem runs through the translational literature and is rarely made explicit. The risk markers are central indices that locate the pituitary set point, whereas the drugs held up as evidence that thyroid signaling can be manipulated therapeutically act mainly on hepatic TRβ. Observational work links reduced central sensitivity to a higher prevalence of metabolic associated fatty liver disease (43), the hepatic condition these drugs target. Resmetirom is the clearest example. In the phase 3 MAESTRO-NASH trial, it resolved NASH and improved fibrosis and lowered LDL cholesterol by roughly 14 to 16 percent (44), and it received accelerated United States approval in 2024 for noncirrhotic NASH with fibrosis (45). This is a genuine success for hepatic TRβ agonism. It does not, however, validate the central indices, because a pituitary set point and hepatic receptor responsiveness are different quantities on different axes. A drug that engages liver TRβ can improve lipids and steatohepatitis whether or not a patient's TFQI is high. Using the marker and the drug to endorse each other is a category error, and it helps explain why an index that predicts risk in observational data may not identify patients who respond to TRβ therapy.

3.3 Incremental prediction

Statistical association does not establish clinical usefulness. A new marker earns a place in assessment only if it improves prediction beyond established variables, assessed through change in the concordance statistic, net reclassification improvement, or integrated discrimination improvement (46). Judged this way, the literature is almost silent. It contains one relevant study, in patients with acute coronary syndrome, in which adding PTFQI to the GRACE score raised the area under the receiver operating characteristic curve for major cardiac and cerebrovascular events from 0.646 to 0.759 (47). A single retrospective analysis reporting area under the curve rather than reclassification metrics does not settle the question. Until several cohorts show consistent incremental gains, these indices remain correlates rather than decision tools.

3.4 Cardiology-specific confounders

For cardiologists, the most practical concern is that the patients we study are exposed to agents that directly alter thyroid tests.

Iodinated contrast given at coronary angiography can transiently perturb thyroid function, amiodarone is rich in iodine and blocks T4-to-T3 conversion, and beta-blockers, glucocorticoids, and acute illness each shift TSH, FT3, or FT4. If blood is drawn shortly after angiography, during amiodarone therapy, or during decompensation, the derived index reflects the exposure rather than a stable trait. Most published studies do not report the timing of sampling relative to these interventions. Added to this is reverse causation: a low FT3 or FT3/FT4 ratio in a patient with coronary or heart failure may be the consequence of subclinical disease, renal impairment, inflammation, or malnutrition. Studies in cardiology populations should therefore document contrast exposure, thyroid-active drugs, and the acute-phase state, and where possible repeat measurements after stabilization. These steps matter more for the validity of the index than refinements to its formula.

4 Conclusions

Sensitivity to thyroid hormone can be approximated in euthyroid people from indices built out of routine tests, but the central indices primarily locate the HPT set point. They have not been validated against tissue responses, they rely on single measurements with appreciable within-person noise, and their apparent multiplicity is largely mathematical rather than biological. Across cardiovascular endpoints, the lipid association is the most consistent and best supported by receptor biology and the RTH phenotype. Associations with arrhythmia, atherosclerosis, hypertension, and heart failure are less stable, mostly cross-sectional, and vulnerable to collider bias, reverse causation, and cardiology-specific exposures such as iodinated contrast and amiodarone. The marker-target mismatch and the near-absence of incremental prediction data further limit clinical use. On present evidence these indices should not guide cardiovascular decisions, but they remain useful for generating hypotheses and selecting participants for confirmatory work.

5 Future directions

Three questions stand between the current literature and clinical use.

The first is whether the indices measure what they claim to. Repeated sampling should establish the within-person stability and intraclass correlation of each index, and studies should test the indices against a physiological reference, such as the tissue response to graded hormone administration. Formulae, cutoffs, and the direction of coding should be standardized so that cohorts can be compared.

The second is causality. Multi-region prospective cohorts and Mendelian randomization should test whether set-point variation predicts incident cardiovascular events, with explicit control for contrast exposure, thyroid-active drugs, and acute illness. Analyses should report whether an index adds to established risk scores using the concordance statistic, net reclassification improvement, and integrated discrimination improvement, rather than association alone.

The third is clinical yield. Intervention trials of tissue-selective thyroid analogs should select patients with a validated marker and be powered for hard outcomes, particularly heart failure hospitalization and survival. Only when measurement, causality, and incremental value are established can thyroid sensitivity move from an observational curiosity to a basis for treatment.

Author contributions

GY: Investigation, Conceptualization, Writing – review & editing, Writing – original draft. YZ: Writing – original draft, Writing – review & editing, Data curation. YB: Data curation, Writing – review & editing, Writing – original draft. PW: Validation, Conceptualization, Supervision, Writing – review & editing, Writing – original draft.

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