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Coffee intake and thyroid function in adults taking levothyroxine: a cross-sectional analysis of NHANES 2007-2012

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Research Article

Keywords: thyroid function, caffeine

Posted Date: November 17th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11733692/v1

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Additional Declarations: The authors declare no competing interests.

Coffee intake and thyroid function in adults taking levothyroxine: a cross-sectional analysis of NHANES 2007–2012

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Running title: Coffee and TSH in levothyroxine users

Keywords: levothyroxine; coffee; thyrotropin; drug–food interaction; NHANES

Abstract

Background: Coffee taken together with levothyroxine (LT4) tablets reduces LT4 absorption in small pharmacokinetic and clinical studies. Whether habitual coffee intake is associated with poorer thyroid hormone replacement in the general population of LT4 users is unknown.

Methods: We analyzed adults aged ≥20 years in the US National Health and Nutrition Examination Survey (NHANES) 2007–2012 who had thyroid function tests and a reliable day-1 24-hour dietary recall. LT4 use was identified from the prescription medication file. Coffee intake (cups/day; 1 cup = 240 g) and the clock time of the first coffee were derived from individual food records. The primary analysis was the design-based, survey-weighted linear regression of log-transformed thyrotropin (TSH) on coffee cups per day among LT4 users, adjusted for age, sex, survey cycle, race/ethnicity, body mass index, serum cotinine, proton pump inhibitor use, use of drugs that bind LT4, and dietary fiber, calcium and iron intake. All other analyses were exploratory.

Results: Of 8,232 eligible adults, 531 used LT4 (78% women; median age 66 years); 16.8% had TSH >4.5 mIU/L and 15.6% had TSH <0.45 mIU/L. In the primary analysis (n = 522), each additional cup of coffee was associated with a 5.7% lower TSH (β = −0.059; 95% CI −0.139 to 0.022; p = 0.15). Coffee intake was not associated with TSH >4.5 mIU/L (odds ratio per cup 0.99; 95% CI 0.77–1.28). In exploratory analyses, LT4 users who drank coffee before 10:00 had lower TSH than those who did not (−33%; p = 0.047), and among coffee drinkers the association of the time of first coffee with TSH differed between LT4 users and non-users (interaction p = 0.018). These exploratory associations were in the direction opposite to impaired absorption and were attenuated without survey weights.

Conclusions: In this nationally representative cross-sectional sample, habitual coffee intake and earlier coffee drinking were not associated with higher TSH or more frequent under-replacement among LT4 users. The findings do not support a population-level adverse effect of coffee on LT4 replacement, but cannot exclude effects that are compensated by dose titration.

Introduction

Levothyroxine (LT4) is one of the most frequently prescribed drugs worldwide, and a substantial proportion of treated patients have serum thyrotropin (TSH) outside the reference range. Because LT4 has a narrow therapeutic index and incomplete, variable intestinal absorption, factors that impair absorption are a recurring clinical concern [1].

Coffee is one such factor. In absorption tests in six women with inadequately controlled TSH and nine volunteers, espresso taken together with LT4 tablets lowered the average incremental rise and the area under the curve of serum thyroxine by 27–36%, whereas espresso taken 60 minutes after LT4 with water did not [2]. Case series and small cohorts have described patients whose TSH improved after coffee or tea was separated from the LT4 dose, and soft-gel and liquid formulations appear less susceptible [3, 4]. Product labels and guidelines therefore advise taking LT4 on an empty stomach, apart from coffee.

These observations come from small, selected groups. In a retrospective study of 150 patients with cardiovascular disease receiving LT4 after thyroidectomy for benign disease, coffee drinking was among the factors examined, and only selective β1-blocker use and smoking were associated with TSH [5]. Whether habitual coffee intake, or drinking coffee in the morning when LT4 is usually taken, is associated with poorer thyroid hormone replacement among LT4 users in the general population is unknown. A previous NHANES analysis of coffee and thyroid function did not exclude or separately analyze LT4 users [6].

We therefore examined, in a nationally representative US sample, whether coffee intake and the timing of the first coffee of the day were associated with TSH and free thyroxine (FT4) among adults taking LT4, and whether any association differed from that in adults not taking thyroid medication.

Methods

Data source

NHANES is a continuous, multistage probability survey of the civilian non-institutionalized US population conducted by the National Center for Health Statistics. We used the three cycles in which thyroid function was measured: 2007–2008, 2009–2010

and 2011–2012. All data are publicly available and de-identified; the NCHS Research Ethics Review Board approved the survey protocols, and participants gave written informed consent.

Study population

Of 11,638 participants with thyroid function data, we included those aged ⩾20 years, not pregnant, not taking antithyroid drugs or thyroid hormone preparations other than LT4, with TSH and FT4 measurements, and with a day-1 dietary recall meeting the minimum NHANES reliability criteria (n = 8,232). We excluded 2,083 participants aged <20 years, 98 pregnant women, 25 users of antithyroid drugs or of thyroid hormone preparations other than LT4, and 1,200 without TSH, FT4 or a reliable recall. LT4 users (n = 531) were participants reporting a prescription medication with the generic name levothyroxine in the 30 days before the interview; the remaining 7,701 participants served as the comparison group. The sample size was fixed by the NHANES thyroid samples, and no formal power calculation was performed.

Exposures

Coffee intake was derived from the day-1 individual foods file as the total grams of foods with USDA food codes beginning 921 (coffee beverages), divided by 240 g to express cups per day. Intake was also categorized as 0, >0–<1, 1–<2 and ⩾2 cups. The clock time of the first coffee was the earliest eating occasion containing coffee; morning coffee was defined as a first coffee before 10:00. Total dietary caffeine (mg/day) was taken from the day-1 total nutrient file.

Outcomes

Serum TSH (mIU/L) and FT4 (ng/dL) were measured in the NHANES laboratory. TSH was log-transformed; coefficients are reported as percentage differences, $(e^{\beta} - 1) \times 100$. Under-replacement was defined as TSH >4.5 mIU/L.

Covariates

Model 1 adjusted for age, sex and survey cycle. Model 2 additionally adjusted for race/ethnicity, body mass index, log serum cotinine, proton pump inhibitor use, use of drugs that may bind LT4 (calcium or iron preparations, bile acid sequestrants, sevelamer, sucralfate, aluminium hydroxide, lanthanum, raloxifene, orlistat), and dietary fiber, calcium and iron intake. Model 2 was the main adjustment set.

Statistical analysis

The primary analysis was the linear regression of log TSH on coffee cups per day (continuous) among LT4 users, adjusted for Model 2 covariates. This designation was made after initial descriptive results were available; the analyses were not preregistered. All other analyses were exploratory: categorical coffee intake, morning coffee, total caffeine, FT4 and TSH >4.5 mIU/L as outcomes; effect modification by LT4 use in the combined sample (coffee × LT4 product term); and, among participants who drank coffee on the recall day, the time of first coffee (before vs after 9:00, 10:00 and 11:00; per hour later; categories; and a quadratic term), further adjusted for cups per day. Sensitivity analyses of the primary model excluded users with TSH <0.1 mIU/L (possible TSH-suppressive therapy), restricted to users treated for ⩾180 days, added log thyroid peroxidase antibody, and omitted survey weights.

We used weighted least squares (linear outcomes) and weighted binomial generalized linear models (TSH >4.5 mIU/L). Weights were the thyroid subsample weights for 2009–2012 and the examination weights for 2007–2008, when thyroid function was measured in the full examination sample, each divided by three to combine cycles. For the primary analysis and its main sensitivity analyses, variances were estimated by Taylor-series linearization with the R package survey (svyglm applied to a subset of the full design, so that domain estimation retained all strata and primary sampling units); confidence intervals used t distributions with the design degrees of freedom. The same estimates were reproduced with an independent Python implementation. Exploratory analyses used cluster-robust standard errors with clusters defined by cycle, masked variance stratum and primary sampling unit, an approximation of the full design. Analyses were complete-case. Given the number of exploratory estimates (about 60), their p values were not adjusted and are interpreted as hypothesis-generating. Analyses used Python 3.13 with pandas, pyreadstat 1.3.7 and statsmodels 0.15, and R with the survey package.

Results

Participants

Of 11,638 participants in the thyroid sample, 8,232 met the inclusion criteria: 531 LT4 users (374, 146 and 101 in the three cycles) and 7,701 non-users. LT4 users were older and more often women, had higher TSH and FT4, and drank slightly more coffee (Table 1). Among users, 16.8% had TSH >4.5 mIU/L and 15.6% had TSH <0.45 mIU/L.

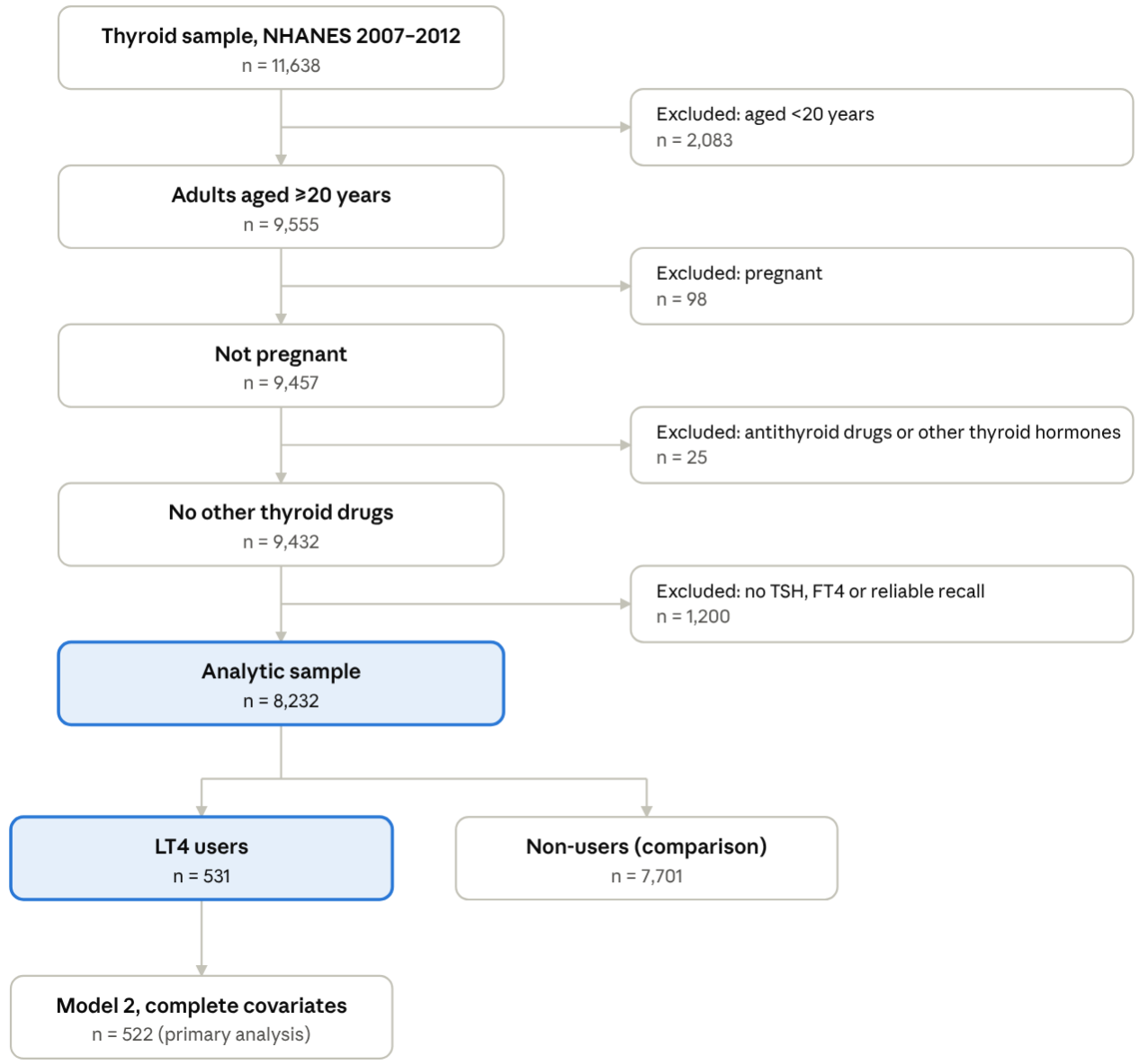


Figure 1 · participant flow

Figure 1. Flow of participants. Of 531 LT4 users, 522 had complete Model 2 covariates and formed the primary analysis set.

Table 1. Characteristics of participants (unweighted).

Characteristic	LT4 users (n = 531)	Non-users (n = 7,701)
Women, %	78.0	47.9
Age, years, median	66	49
Body mass index, kg/m², median	28.9	27.9

Characteristic	LT4 users (n = 531)	Non-users (n = 7,701)
TSH, mIU/L, median	1.95	1.55
TSH >4.5 mIU/L, %	16.8	3.9
TSH <0.45 mIU/L, %	15.6	2.8
FT4, ng/dL, median	0.9	0.8
Any coffee on recall day, %	64.4	53.2
Coffee, cups/day, median	1.05	0.65
First coffee before 10:00, %	53.7	42.7
Dietary caffeine, mg/day, median	110	101
Proton pump inhibitor use, %	21.3	8.7
LT4-binding drug use, %	4.7	2.0
Duration of LT4 use, days, median	3,650	—

Missing data: 9 of 531 LT4 users lacked at least one Model 2 covariate (n = 522 in Model 2), and 500 of these 522 had thyroid peroxidase antibody data.

Primary analysis

Among 522 LT4 users with complete covariates, each additional cup of coffee per day was associated with a 5.7% lower TSH (β = −0.059; design-based 95% CI −0.139 to 0.022; p = 0.15; 44 degrees of freedom). The cluster-robust approximation gave nearly identical results (95% CI −0.137 to 0.019; p = 0.14), and the unadjusted estimate was similar (−5.2% per cup; 95% CI −0.146 to 0.040; p = 0.25). Results were similar in all sensitivity analyses; the association was statistically significant only without survey weights (Table 2). Among non-users, the corresponding estimate was −0.7% per cup (p = 0.24), and the coffee × LT4 interaction was not significant (p = 0.15).

Table 2. Coffee cups per day and log TSH among LT4 users: primary and sensitivity analyses.

Analysis	n	β (95% CI)	TSH difference per cup	p
Primary (Model 2)	522	−0.059 (−0.139, 0.022)	−5.7%	0.15
Unadjusted	531	−0.053 (−0.146, 0.040)	−5.2%	0.25

Analysis	n	β (95% CI)	TSH difference per cup	p
Model 1	531	−0.057 (−0.138, 0.025)	−5.5%	0.17
Excluding TSH <0.1 mIU/L	493	−0.047 (−0.111, 0.017)	−4.6%	0.15
LT4 use ⩾180 days	493	−0.059 (−0.139, 0.021)	−5.7%	0.15
Adding log TPO antibody	500	−0.060 (−0.139, 0.019)	−5.8%	0.14
Unweighted	522	−0.072 (−0.135, −0.009)	−7.0%	0.025
Non-users (Model 2)	7,615	−0.007 (−0.019, 0.005)	−0.7%	0.24
Interaction coffee × LT4	8,137	−0.062 (−0.147, 0.023)	—	0.15

Primary and unadjusted rows: design-based 95% CI and p value (Taylor linearization, R survey package; 44 degrees of freedom). Other rows: cluster-robust approximation of the survey design. Design-based estimates for Model 1 (p = 0.20), exclusion of TSH <0.1 mIU/L (p = 0.16), non-users (p = 0.20) and the interaction (p = 0.17) were consistent with those shown.

Exploratory analyses

Coffee intake was not associated with under-replacement (TSH >4.5 mIU/L: OR per cup 0.99; 95% CI 0.77–1.28; p = 0.94) and total caffeine intake was not associated with TSH (p = 0.20). FT4 was 0.012 ng/dL higher per cup (95% CI 0.0003–0.024; p = 0.044). Users with a first coffee before 10:00 had 33% lower TSH than other users, including non-drinkers (p = 0.047), and this difference was specific to LT4 users (interaction p = 0.045).

Among coffee drinkers, LT4 users (n = 342) drank their first coffee at a median of 8:00 (interquartile range 7:00–9:00); 108 before 7:00, 164 at 7:00–8:59, 52 at 9:00–11:59 and 18 at or after 12:00. Adjusted for cups per day, none of the timing variables was significantly associated with TSH within users, but the association of timing with TSH differed between users and non-users (Table 3). Timing was not associated with FT4 or TSH >4.5 mIU/L.

Table 3. Exploratory analyses of coffee timing and log TSH (Model 2 plus cups per day for timing analyses).

Analysis	n	β (95% CI)	TSH difference	p
All users: ⩾2 vs 0 cups/day	522	−0.435 (−0.903, 0.033)	−35%	0.069
All users: first coffee before 10:00 (vs not)	522	−0.401 (−0.797, −0.005)	−33%	0.047
Interaction before 10:00 × LT4, all participants	8,137	−0.424 (−0.838, −0.010)	—	0.045
Drinkers, users: first coffee before 10:00 vs later	338	−0.522 (−1.116, 0.071)	−41%	0.084
Drinkers, users: before 9:00 vs later	338	−0.422 (−0.885, 0.041)	−34%	0.074
Drinkers, users: before 11:00 vs later	338	−0.208 (−0.898, 0.482)	−19%	0.55
Drinkers, users: per hour later	338	0.063 (−0.018, 0.143)	+6.5%	0.13
Same, excluding TSH <0.1 mIU/L	319	0.036 (−0.017, 0.089)	+3.7%	0.18
Same, unweighted	338	0.019 (−0.039, 0.077)	+1.9%	0.52
Drinkers, non-users: per hour later	4,053	0.003 (−0.011, 0.017)	+0.3%	0.67
Drinkers: interaction before 10:00 × LT4	4,391	−0.595 (−1.133, −0.057)	—	0.030
Drinkers: interaction per hour × LT4	4,391	0.073 (0.013, 0.134)	—	0.018

Discussion

In this nationally representative sample of US adults taking LT4, habitual coffee intake was not associated with higher TSH or with more frequent under-replacement. The point estimate of the primary analysis indicated slightly lower, not higher, TSH with more coffee, and exploratory analyses of morning coffee and of the timing of the first coffee pointed in the same direction. These findings do not support the hypothesis that coffee, as consumed in daily life, impairs LT4 replacement at the population level.

Our results do not contradict the pharmacokinetic evidence. The reduction in LT4 absorption has been shown when coffee is taken together with the tablet, and not when it is taken an hour later [2]. In routine care, many patients are advised to separate LT4 from coffee, and any residual malabsorption is likely to be detected by TSH monitoring and offset by dose titration. A cross-sectional survey cannot see this compensated state: two patients with the same TSH may need different doses. The absence of an association with TSH therefore means that coffee drinkers are not, on average, less well controlled, not that coffee has no effect on absorption.

The exploratory finding that early coffee drinking was associated with lower TSH specifically in LT4 users requires caution. Within users, none of the timing estimates reached statistical significance, the estimates were attenuated without survey weights, the late-drinking group was small, and about 60 exploratory estimates were obtained. If the association is real, several explanations are possible. A regular morning routine that includes coffee may also favour regular LT4 intake, so that adherence confounds the association. Alternatively, a central effect of caffeine on TSH secretion would be expected to appear more clearly in LT4-dependent patients, whose thyroid hormone supply is fixed by the dose and cannot rise or fall in response to TSH, than in people with an intact thyroid, in whom a small change in TSH is buffered by feedback. In rats, a single dose of caffeine lowered serum TSH dose-dependently for up to 6 hours, whereas caffeine applied directly to pituitaries in vitro did not change hormone secretion, suggesting a central action [7]. Caffeine antagonizes adenosine receptors and increases sympathetic and dopaminergic activity; dopamine suppresses TSH release [8], and adrenergic, cAMP-dependent signalling activates type 2 deiodinase, which converts T4 to T3 [9]. These mechanisms are speculative here and were not tested. Coffee consumed shortly before the blood draw could also have acute effects on TSH. We attempted to examine this using the NHANES fasting questionnaire, but only 1 of 531 LT4 users and 31 of 7,701 non-users reported coffee or tea within 8 hours before the examination, so acute effects could not be assessed.

Strengths of this study include a nationally representative sample with laboratory-measured thyroid function, identification of LT4 use from interviewer-recorded prescription medication data, individual food records that allowed both the amount and the clock time of coffee to be estimated, and a comparison group of non-users that allowed effect modification to be tested.

Limitations

First, the design is cross-sectional and causal inference is not possible. Second, NHANES does not record LT4 dose, dose changes, time of LT4 intake, adherence or formulation; we could therefore not assess whether coffee was taken close to the LT4 dose, and nearly all users in 2007–2012 would have used tablets. Third, coffee intake was estimated from a

single 24-hour recall, which measures habitual intake with error and attenuates associations. Fourth, the indication for LT4 (e.g., Hashimoto thyroiditis, thyroidectomy, thyroid cancer) is unknown; users with TSH <0.1 mIU/L were excluded in a sensitivity analysis as a proxy for TSH-suppressive therapy. Fifth, exploratory analyses used cluster-robust approximations of the survey design and weighted logistic estimates are approximate; in a design-based analysis, the morning-coffee estimate among users was p = 0.053 rather than 0.047. Sixth, the primary analysis was designated after initial results were available and was not preregistered, and exploratory p values were not adjusted for multiple comparisons. Seventh, the fasting questionnaire asks about coffee or tea with cream or sugar and may not capture black coffee, and almost no participants reported such intake within 8 hours of the examination; the acute effect of coffee at the time of blood sampling therefore remains unknown. Residual confounding by health behaviours and comorbidities cannot be excluded. Finally, the results apply to US adults using LT4 tablets in 2007–2012 and may not apply to populations with different coffee-drinking habits or to soft-gel or liquid formulations.

Conclusions

Among US adults taking LT4, habitual coffee intake and earlier coffee drinking were not associated with higher TSH or under-replacement. At the population level, coffee does not appear to compromise LT4 replacement as managed in routine care, although effects that are compensated by dose titration cannot be excluded. Longitudinal studies that record LT4 dose, the timing of LT4 and coffee, and formulation are needed to determine whether coffee increases dose requirements.

Declarations

Ethics approval: NHANES protocols were approved by the NCHS Research Ethics Review Board. This secondary analysis of public, de-identified data did not require additional approval.

Data availability: NHANES data are publicly available from the National Center for Health Statistics (https://wwwn.cdc.gov/nchs/nhanes/). The analysis code (Python and R) is provided as supplementary material.

Funding: This study received no funding. The author did not receive payment or services from a third party for any aspect of the submitted work.

Competing interests: The author declares no competing interests. The author and the author's institution did not receive payments or services from a third party in the past 36 months that could be perceived to influence, or give the appearance of potentially influencing, the submitted work.

Author contributions: KO conceived the study, conducted the analysis, interpreted the results and wrote the manuscript.

Use of AI tools: An AI assistant (Claude, Anthropic) was used to write analysis code and to draft the manuscript; the author verified the analyses and takes full responsibility for the content.

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