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Modification of TSH-related genetic effects by indicators of socioeconomic position

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Abstract

Objective: Thyroid-stimulating hormone (TSH) is influenced by genetic and environmental factors such as socioeconomic position (SEP). However, interactions between TSH-related genetic factors and indicators of SEP have not been investigated to date. The aim of the study was to determine whether education and income as SEP indicators may interact with TSH-related genetic effect allele sum scores (GES_{TSH_2013} and GES_{TSH_2020}) based on two different GWAS meta-analyses that affect TSH values in a population-based study.
Methods: In 4085 participants of the Heinz Nixdorf Recall Study associations between SEP indicators, GES_{TSH} and TSH were quantified using sex- and age-adjusted linear regression models. Interactions between SEP indicators and GES_{TSH} were assessed by GES_{TSH} × SEP interaction terms, single reference joint effects and calculating genetic effects stratified by SEP group.
Results: Participants within the highest education group showed the strongest genetic effect with on average 1.109-fold (95% CI: 1.067–1.155) higher TSH values per GES_{TSH_2013} SD, while in the lowest education group, the genetic effect was less strong (1.061-fold (95% CI: 1.022–1.103)). In linear regression models including interaction terms, some weak indication for a positive GES_{TSH_2013} by education interaction was observed showing an interaction effect size estimate of 1.005 (95% CI: 1.000–1.010) per year of education and GES_{TSH_2013} SD. No indication for interaction was observed for using income as SEP indicator. Using the $GES_{TSH\_2020,}$ similar results were observed.
Conclusion: Our results gave some indication that education may affect the expression of TSH-related genetic effects. Stronger genetic effects in high-education groups may be explained by environmental factors that have an impact on gene expression and are more prevalent in high SEP groups.

Key Words

- thyroid-stimulating hormone
- socioeconomic position
- genetics
- gene-environment interaction

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Introduction

Thyroid hormones play an important role in almost all biological processes in humans such as energy metabolism, cell growth, development, cardiovascular system, CNS, immunity and bone metabolism (1, 2). Importantly, several studies have shown associations between overt or subclinical thyroid dysfunction and clinical endpoints such as cardiovascular disease, atrial fibrillation (3), dyslipidaemia (3), hypertension (4), atherosclerosis (5), type 2 diabetes (3) and bone fractures (6). Even psychological symptoms such as depression (7) or reduced quality of life (8) are associated with subclinical thyroid dysfunction. Because thyroid-stimulating hormone (TSH) reacts strong to minor changes in thyroid hormone values, abnormal TSH values are more sensitive markers for early thyroid dysfunction including hypothyroidism as well as hyperthyroidism than the measurement of

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thyroid hormones values (9). Further, it has been reported that thyroid function is influenced by genetic variation as well as social factors such as socioeconomic position (SEP), both contributing to substantial inter-individual differences observed in healthy populations (10, 11, 12). For instance, Völzke *et al.* (13) have detected higher TSH values in unemployed participants compared to employed participants in a population-based cohort. In addition, it has been indicated that there is a greater chance of developing thyroid dysfunction with lower income and higher deprivation levels (10, 12), while higher education may reduce the risk for low TSH values (14).

While every human has an individual hypothalamic–pituitary–thyroid axis setpoint within a range that is predominately determined by genes mainly responsible for intra-individual differences (15), twin studies have also suggested a heritability of 57–71% for inter-individual variance in TSH serum values (16, 17). Genome-wide association studies (GWAS) have already identified genetic loci that are associated with thyroid function. Porcu *et al.* (2013) (18) performed a GWAS on TSH values within the normal range in over 25,000 participants and found 20 robustly associated genetic loci, which explained 5.6% of the total variation in serum TSH values of the study population. In a more recent GWAS, Zhou *et al.* (2020) (19) identified 74 genome-wide significant loci, which had on average weaker individual effects on TSH compared to previous GWAS results, but explained 13.3% of the total variation in serum TSH values. Results have also suggested that the total genetic effect on TSH is determined by many common genetic variants with a small individual effect (15). While it has been hypothesised that interactions between genetic and environmental factors (G×E) may partly account for the missing heritability of common traits and the low penetrance of single common genetic variants (20), interactions between TSH-related genetic factors and indicators of SEP have not been studied to date.

The aim of the present study was to examine whether SEP indicators' education and income interact with TSH-related genetic effect allele sum scores to affect TSH serum values in a population-based study.

Material and methods

Study population

All analyses were based on the population-based Heinz Nixdorf Recall Study. From December 2000 to August 2003, a total of 4814 participants aged 45–75 years were randomly selected and recruited from mandatory citizen registries of the three cities Bochum, Essen and Mülheim/Ruhr. These cities are located in the Western part of Germany. The baseline response proportion was 55.8% (21). More information about the study design has been provided in detail elsewhere (22). The study was approved by the local ethics committee of the University of Duisburg-Essen. The study involves extended quality management procedures with a certification to DIN ISO 9001:2000. All participants gave written informed consent.

Indicators of socioeconomic position

Education and income were used as indicators of SEP. Information was collected at study baseline by using standardised computer-assisted face-to-face interviews. The International Standard Classification of Education (ISCED) was used to define education as total years of formal education by combining school and vocational training (23). It was then either used as continuous variable or categorised into four groups for stratified analyses with the lowest group of ≤10 years of education, which is equivalent to a basic school degree with no vocational training, and the highest group of ≥18 years of education, which is equivalent to a university degree. Income was measured as the monthly household equivalent income calculated by dividing the participants' household net income by a weighting factor for each household member. Income was used as a continuous variable or was categorised into sex-specific quartiles. Education and income were analysed separately to consider their different mechanism in causing social inequalities in health (24, 25).

TSH

Serum TSH values were assessed from frozen blood samples with the Roche Modular Analytics E170 electro-chemiluminescence immunoassay (Roche Diagnostic). The working range for this method was 0.005–100 mIU/L. The functional sensitivity amounts to 0.014 mIU/L. TSH values were used as a continuous variable except for some of the analysis, for which, the main analysis population was categorised into euthyroid, hypothyroid and hyperthyroid participants. The reference range of 0.27–4.20 mIU/L by the manufacturer was adopted to define participants as euthyroid. Hyperthyroid status was defined as TSH values <0.27 mIU/L, while hypothyroid status was defined as TSH values >4.20 mIU/L.

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Genetic data

Lymphocyte DNA was isolated from EDTA anti-coagulated venous blood using the Chemagic Magnetic Separation Module I (Chemagen, Baesweiler, Germany). The meta-analyses of genome-wide association studies by Porcu *et al.* (2013) (18) and Zhou *et al.* (2020) (19) were used to identify lead single nucleotide polymorphisms (SNPs) representing independent genetic loci robustly associated with TSH on the global screening array 24v1.0 available for all study participants included in the analysis (Supplementary Tables 1 and 2, see section on supplementary materials given at the end of this article). Genotype imputation was carried out using IMPUTE version 2 (v.2.3.1) (26, 27) with reference data from 1000 Genomes Phase 1 (v3). No deviation from Hardy–Weinberg equilibrium (HWE) ($P \leq 0.001$) was detected. To compare the genetic effects from two different GWAS meta-analyses that reflect differences in the average individual effect size of the reported genome-wide significant SNPs, two weighted genetic effect allele sum scores (i.e. GES_{TSH_2013} including 19 SNPs based on the Porcu *et al.* meta-analysis and GES_{TSH_2020} including 126 SNPs based on the Zhou *et al.* meta-analysis) were calculated by aggregating the total number of TSH increasing alleles for each individual across the selected SNPs using the software PRSice-2 (28). Both scores were weighted by the corresponding effect-size estimate of each SNP reported in the literature. For SNP clumping, a linkage disequilibrium (LD) cut-off of $r^2 = 0.1$ was used. To reflect the number of TSH-increasing alleles, both GES were rescaled by multiplying the weighted sum score by the number of SNPs included and then dividing it by the sum of effect-size estimates of the SNPs reported in the respective meta-analysis. For comparing results between both GES, effect size estimates were reported per S.D. of the respective GES. Participants of the Heinz Nixdorf Recall Study are of European ancestry and genetically homogeneous.

Statistical analysis

Out of the baseline study population, 4085 participants were included in the main analysis population, as participants with missing genetic information or missing TSH values were excluded from analysis. In addition, two participants with TSH values > 80 mIU/L were excluded to avoid extreme outliers. For sensitivity analysis, additional 1293 participants reporting a history of thyroid dysfunction (including thyroid cancer or thyroid removal) or intake of thyroid medication were excluded (Fig. 1).

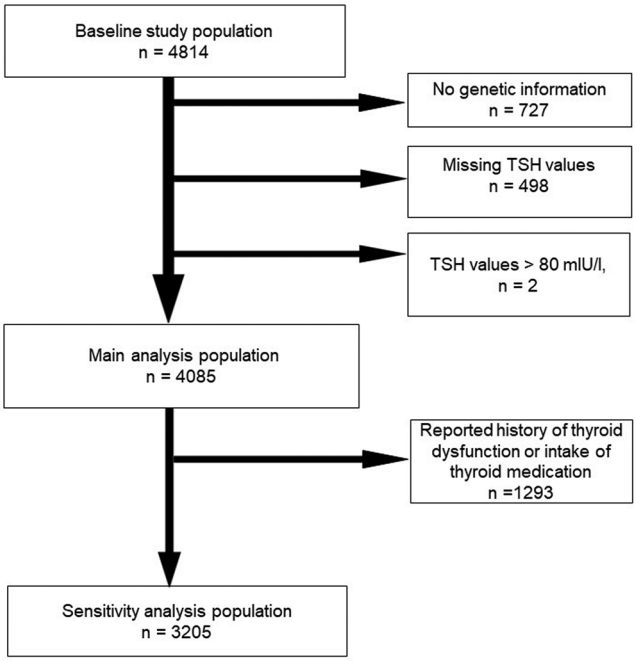

Figure 1
Flowchart of participants out of the Heinz Nixdorf Recall study included in the analysis.

For statistical analysis, TSH values were log-transformed using the natural logarithm to normalise the distribution. To prevent numerical errors, the TSH values were corrected by adding 1 before log-transformation (ln(TSH+1)). Results of linear regression analysis were back-transformed and reported as Exp(β) with 95% CI. Exp(β) can be interpreted as the factor change of the geometric mean (TSH+1) value per unit change of the independent variable, while it has to be stated that the addition of the relatively high value of 1 to TSH prior to log-transformation limits the interpretation of the obtained effect size estimates as relative change. To assess the associations of SEP indicators and the GES_{TSH_2013}/GES_{TSH_2020} with TSH values, linear regression analysis with continuous ln(TSH+1) as dependent variable was performed. In addition, associations of SEP indicators with thyroid status (euthyroid/hypothyroid/hyperthyroid) as dependent variable were assessed using logistic regression analysis in order to account for a possible U-shaped relationship between SEP and TSH. In the logistic regression analyses, the thyroid status was set as the dependent variable with euthyroid participants as the reference group and either hyperthyroid or hypothyroid participants as cases. Further, sex-stratified analyses were performed.

The main effect of the GES_{TSH_2013}/GES_{TSH_2020} on TSH was calculated using linear regression models with continuous ln(TSH+1) as dependent variable. The effect of

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Table 1 Characteristics of main analysis population stratified by sex.

	All (*n* = 4085)	**Men** (*n* = 2039)	**Women** (*n* = 2046)
Age (years)[a]	59.7 ± 7.8	59.7 ± 7.8	59.7 ± 7.8
Income (€/month) [c] n_{miss}=258	1448 (1107–1874)	1520 (1107–2072)	1278 (937–1874)
Lowest income quartile	1206 (31.5%)	518 (26.5%)	688 (36.7%)
Second income quartile	885 (23.1%)	422 (21.6%)	463 (24.7%)
Third income quartile	533 (13.9%)	294 (15.0%)	239 (12.8%)
Highest income quartile	1203 (31.4%)	720 (36.8%)	483 (25.8%)
Education (years of training) [b] n_{miss}=12			
≤10 years	474 (11.6%)	97 (4.8%)	377 (18.4%)
11–13 years	2249 (55.2%)	971 (47.9%)	1278 (62.5%)
14–17 years	922 (22.6%)	687 (33.9%)	235 (11.5%)
≥18 years	428 (10.5%)	274 (13.5%)	154 (7.5%)
TSH values (mIU/L)[c]	1.26 (0.83–1.84)	1.24 (0.87–1.74)	1.28 (0.77–1.94)
Hyperthyroid (TSH value <0.27 mIU/L)[b]	183 (4.5%)	50 (2.5%)	133 (6.5%)
Hypothyroid (TSH value >4.2 mIU/L)[b]	120 (2.9%)	35 (1.7%)	85 (4.2%)
Thyroid medication	525 (12.9%)	89 (4.4%)	436 (21.3%)
TSH-associated genetic effect allele sum score (GES_{TSH_2013})[a]	24.7 ± 2.7	24.7 ± 2.7	24.6 ± 2.7
TSH-associated genetic effect allele sum score (GES_{TSH_2020})[a]	32.3 ± 4.6	32.3 ± 4.5	32.3 ± 4.6

[a]Mean ± s.d.; [b]*n* (%); [c]Median (first quartile to third quartile).
n_{miss}, number of participants with missing values.

GES_{TSH_2013}/GES_{TSH_2020} on TSH was also stratified by education groups and income quartiles to assess heterogeneity of the genetic effect across SEP strata. Additionally, sex-stratified analysis of the effect of GES_{TSH_2013}/GES_{TSH_2020} on TSH was performed. The GES_{TSH_2013} was then divided into tertiles and all possible combinations of GES_{TSH_2013} tertiles and SEP indicators were entered as dummy variables into a linear regression model with the group of lowest GES_{TSH_2013} and lowest education or income as reference to analyse single reference joint effects between the genetic effect and SEP indicators on TSH. In addition, linear regression models were fitted including GES_{TSH_2013}/GES_{TSH_2020} by SEP indicator interaction terms. All regression models were adjusted for sex and age to control for confounding. Statistical analyses were performed using the SPSS software (SPSS Inc., version 27.0).

Results

Half of the study participants were women (Table 1). The mean (±s.d.) age of the main analysis population was 59.7 ± 7.8 years. The median TSH value in this main analysis population was 1.26 mIU/L (interquartile range: 0.83–1.84). Men and women did not differ strongly in median TSH values in the study population. However, there was a substantial difference between men and women in SEP. As compared to women, men were on average higher educated and had a higher household income in the study population.

The calculation of the association between GES_{TSH_2013} and TSH showed an on average 1.088-fold (95% CI: 1.073–1.100) higher TSH value per standard deviation of the GES_{TSH_2013} (Table 2), while for the GES_{TSH_2020}, similar results were observed (Supplementary Table 3). An insignificantly stronger GES_{TSH_2013} effect was observed for men compared to women in the study population (Supplementary Table 4). An association between SEP

Table 2 Sex- and age-adjusted effects (Exp(β)) and corresponding 95% CIs on thyroid-stimulating hormone (TSH) values in separate linear regression models including main effects of education (per year) and income (per 1000 €/month) as indicators of socioeconomic position (SEP) and a TSH-associated genetic effect allele sum score (GES_{TSH_2013}; per s.d.).

	Exp(β) (95% CI)	***P***
Education		
Sex (female)	1.015 (0.989–1.041)	0.25
Age	1.000 (0.998–1.001)	0.84
Education (per year)	0.997 (0.991–1.002)	0.22
Income		
Sex (female)	1.021 (0.996–1.048)	0.10
Age	1.000 (0.998–1.002)	0.92
Income (per 1000 €/month)	1.000 (0.982–1.018)	0.99
GES_{TSH_2013}		
Sex (female)	1.022 (0.998–1.047)	0.07
Age	1.000 (0.999–1.002)	0.91
GES_{TSH_2013} (per s.d.)	1.088 (1.073–1.100)	2.1×1^{-42}

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Table 3 Odds ratios (OR) and 95% CIs for the association of income (per 1000 €/month) and education (per year) with hyperthyroid vs euthyroid status.

	OR (95% CI)	***P***
Education		
Hyperthyroid ~ education		
Education (per year)	0.918 (0.862–0.979)	8.7×10^{-3}
Hyperthyroid ~ education + age + sex		
Education (per year)	0.999 (0.932–1.070)	0.97
Age	1.024 (1.004–1.044)	0.02
Sex (female)	2.830 (1.996–4.014)	5.3×10^{-9}
Income		
Hyperthyroid ~income		
Income (per 1000 €/month)	0.736 (0.581–0.932)	0.01
Hyperthyroid ~ income + age + sex		
Income (per 1000 €/month)	0.840 (0.662–1.065)	0.15
Age	1.020 (1.000–1.040)	0.05
Sex (female)	2.845 (2.014–4.019)	3.0×10^{-9}

Table 4 Odds ratios (OR) and 95% CIs for the association of income (per 1000 €/month) and education (per year) with hypothyroid vs euthyroid status.

	OR (95% CI)	***P***
Education		
Hypothyroid ~ education		
Education (per year)	0.875 (0.808–0.947)	9.9×10^{-4}
Hypothyroid ~ education + age + sex		
Education (per year)	0.921 (0.846–1.004)	0.06
Age	0.997 (0.974–1.021)	0.82
Sex (female)	2.286 (1.505–3.472)	1.0×10^{-4}
Income		
Hypothyroid ~ income		
Income (per 1000 €/month)	0.771 (0.582–1.023)	0.07
Hypothyroid ~ income+ age + sex		
Income (per 1000 €/month)	0.842 (0.634–1.119)	0.24
Age	0.999 (0.975–1.023)	0.91
Sex (female)	2.636 (1.743–3.988)	4.0×10^{-6}

indicators and TSH could not be observed (Table 2). Using categorical TSH as dependent variable in logistic regression analysis, there was some indication for an association of education and income, having TSH values outside of the reference range in crude regression models (Table 3 and 4). However, results after adjustment for age and sex indicated that this association was mainly explained by confounding while female sex was associated with having TSH values outside of the reference range in all regression models.

In stratified analyses, the effect of GES_{TSH_2013} on TSH increased with increasing education levels (Fig. 2). Participants with the lowest education (≤10 years) had the weakest genetic effect with on average 1.061-fold (95% CI: 1.022–1.103) higher TSH values per s.d. of the GES_{TSH_2013}, while participants with the highest education (≥18 years) had the strongest genetic effect with on average 1.109-fold (95% CI: 1.067–1.155) higher TSH values per SD. Although a trend of increasing genetic effects on TSH with increasing income quartile was indicated, the differences between income quartiles were less marked. Overall, results showed a positive trend in the genetic main effect on TSH across education groups.

The analysis of joint effects between SEP and GES_{TSH_2013} categories revealed a clear trend within but not

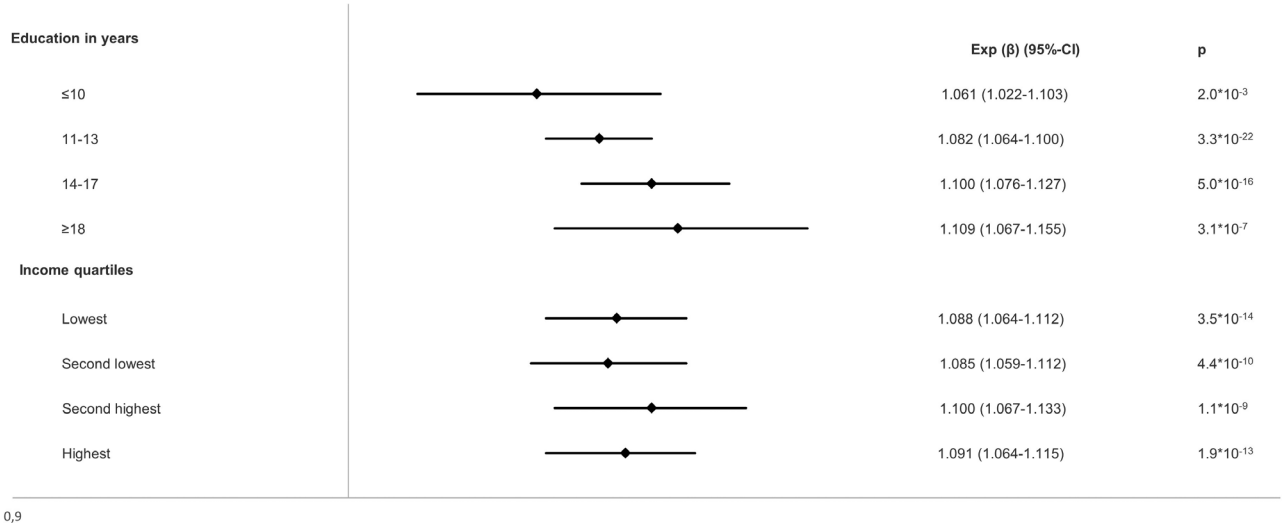

Figure 2
Sex-and age-adjusted effects and corresponding 95% CI of the genetic effect per standard deviation (GES_{TSH_2013}) on thyroid-stimulating hormone (TSH) values stratified by education groups (in years) and income quartiles in linear regression models.

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Table 5 Sex- and age-adjusted effects (Exp(β)) and corresponding 95% CIs on thyroid-stimulating hormone (TSH values) in linear regression models of the joint effects of tertiles of a TSH-associated effect allele sum score (GES_{TSH_2013}) and socioeconomic position indicators, calculated separately for income quartiles and education categories with the group of having a low genetic effect allele sum score and the lowest socioeconomic position as reference.

	n	**Exp**(β) (95% CI)	*P*
Education/GES_{TSH_2013} groups			
≤10 years			
Low GES_{TSH_2013}	159	Reference category	Reference category
Middle GES_{TSH_2013}	162	1.223 (0.970–1.543)	0.09
High GES_{TSH_2013}	153	1.518 (1.200–1.925)	5.1×10^{-4}
11–13 years			
Low GES_{TSH_2013}	737	0.946 (0.790–1.136)	0.56
Middle GES_{TSH_2013}	749	1.184 (0.986–1.418)	0.07
High GES_{TSH_2013}	763	1.526 (1.275–1.833)	5.0×10^{-6}
14-17 years			
Low GES_{TSH_2013}	317	0.839 (0.686–1.027)	0.09
Middle GES_{TSH_2013}	291	1.146 (0.934–1.406)	0.19
High GES_{TSH_2013}	314	1.506 (1.230–1.848)	7.2×10^{-5}
≥18 years			
Low GES_{TSH_2013}	147	0.858 (0.674–1.088)	0.20
Middle GES_{TSH_2013}	159	1.177 (0.931–1.485)	0.17
High GES_{TSH_2013}	122	1.564 (1.217–2.011)	4.6×10^{-4}
Income/GES_{TSH_2013} groups			
Lower quartile			
Low GES_{TSH_2013}	400	Reference category	Reference category
Middle GES_{TSH_2013}	399	1.187 (1.027–1.376)	0.02
High GES_{TSH_2013}	407	1.684 (1.457–1.951)	2.7×10^{-12}
Second quartile			
Low GES_{TSH_2013}	279	0.921 (0.784–1.082)	0.32
Middle GES_{TSH_2013}	304	1.306 (1.115–1.530)	8.9×10^{-4}
High GES_{TSH_2013}	302	1.497 (1.278–1.754)	6.0×10^{-7}
Third quartile			
Low GES_{TSH_2013}	179	0.957 (0.795–1.152)	0.64
Middle GES_{TSH_2013}	170	1.036 (0.858–1.254)	0.71
High GES_{TSH_2013}	184	1.652 (1.376–1.989)	9.7×10^{-8}
Highest quartile			
Low GES_{TSH_2013}	416	0.931 (0.806–1.076)	0.34
Middle GES_{TSH_2013}	414	1.313 (1.136–1.518)	2.3×10^{-4}
High GES_{TSH_2013}	373	1.608 (1.387–1.868)	4.7×10^{-10}

between the different SEP/GES_{TSH_2013} groups (Table 5). Regarding the analysis of education, the joint effect was the strongest in the group with high GES_{TSH_2013} in the highest education group, with on average 1.564-fold (95% CI: 1.217–2.011) higher TSH values compared to the reference category of low education and low GES_{TSH_2013}.

Linear regression models including interaction terms between SEP indicators and the GES_{TSH_2013} gave some weak indication for GES_{TSH_2013} by education interaction showing an effect size estimate for the interaction term of 1.005 (95% CI: 1.000–1.010) per year of education and S.D. of the GES_{TSH_2013}. No indication for a GES_{TSH_2013} by income interaction was observed, although the direction of the effect size estimate (1.008 (95% CI: 0.991–1.027) per 1000 €/month and S.D. of the GES_{TSH}) was consistent with the observed GES_{TSH_2013} by education interaction (Table 6). The effect size estimates for the observed GES_{TSH_2013} by education interaction were slightly stronger in men compared to women (Supplementary Table 5) and slightly stronger compared to the GES_{TSH_2020} by education interaction effect size estimate (Supplementary Table 6).

In the sensitivity analysis, participants were excluded if they had a positive history of thyroid dysfunction or reported taking medications that affect the thyroid gland. Thus, three times more women than men were excluded (Supplementary Table 7). Overall, effect size estimates of the main results did not differ compared to the main analysis population (Supplementary Tables 8, 9 and Supplementary Fig. 1). However, due to the smaller sample size in the sensitivity analysis, the precision of the effect size estimation was decreased, leading to wider 95% CIs.

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Table 6 Sex- and age-adjusted effects (Exp(β)) and corresponding 95% CIs on thyroid-stimulating hormone (TSH values) in linear regression models including interaction terms of a TSH-associated genetic effect allele sum score (GES_{TSH_2013}; per S.D.), education (per years of education) and income (per 1000 €/month) as indicator of socioeconomic position.

	Exp(β) (95% CI)	***P***
Education		
Sex (female)	1.019 (0.994–1.044)	0.14
Age	1.000 (0.998–1.001)	0.93
Education (per year)	0.953 (0.910–0.997)	0.04
GES_{TSH_2013}	1.013 (0.944–1.085)	0.72
GES_{TSH_2013} × education	1.005 (1.000–1.010)	0.045
Income		
Sex (female)	1.024 (0.999–1.050)	0.06
Age	1.000 (0.998–1.002)	0.96
Income (per 1000 €/month)	0.920 (0.785–1.078)	0.31
GES_{TSH_2013}	1.073 (1.041–1.106)	2.0×10^{-6}
GES_{TSH_2013} × income	1.008 (0.991–1.027)	0.29

Discussion

The results of the present study gave some indication that SEP indicator educational attainment may affect serum TSH values by interacting with a TSH-related weighted genetic effect allele sum score. With higher education, a stronger effect of the GES_{TSH_2013} on TSH values was observed. This is supported by education-stratified analyses of the genetic effect on TSH values. Also, joint effects of all possible combinations of GES_{TSH_2013} tertiles and education groups showed the strongest effect on TSH values for participants with the highest GES_{TSH_2013} within the highest education group. Effect size estimates for the GES_{TSH_2013} by education interaction term gave some support for interaction. Results for the GES_{TSH_2020} showed slightly less strong effect size estimates. This may reflect the on-average weaker effects of individual SNP on TSH in the GES_{TSH_2020}.

The direction of the GES_{TSH_2013} main effect on TSH was consistent with previous studies conducted by Porcu *et al.* and Chaker *et al.* (18, 29). In these studies, the same set of SNPs has been used in a polygenic risk score. Importantly, the genetic effect in our study differs only slightly between sexes. A stronger genetic effect in men has been explained by sex-specific strength of effects of genetic loci included in the GES_{TSH_2013}. Porcu *et al.* (18) detected that TSH-elevating alleles in gene MAF/LOC440389 and gene PDE10A were related to a stronger TSH increase in men, while this sex difference did not replicate in the extended GWAS of Teumer *et al.* (2018) (30) Interestingly, recent studies have reported that women showed a higher heritability for TSH values compared to men (31, 32). An explanation for this result might be that the previously identified loci just explain a fraction of the total variation in serum TSH values indicating substantial missing heritability. Thus, the exact nature of sex differences in the genetic effects on TSH might not be fully reflected by the GES_{TSH} used in the present study.

Sex and age are potential confounders for the association between SEP and thyroid function. In the present study, an association was observed between female sex having TSH values outside the reference range, which is in line with previous studies (10, 33, 34, 35). Associations between age and TSH values have been discussed controversially in the literature. Similar to the present study, some studies have shown no indication of an association between age and TSH (36, 37). In contrast, an increase in TSH values with increasing age was observed in other studies (38, 39). These discrepancies may be due to the age structure of each cohort and regional differences in iodine supply.

Having a higher income or more years of education has been reported to decrease the chance of being hypothyroid or hyperthyroid depending on serum TSH values in previous studies, even though this association was not strongly indicated and confounded by age and sex in the present study. Santos Palacios *et al.* (10) suggested that the risk of developing hyper- or hypothyroidism may be reduced with increasing income. Other studies have shown that higher education is associated with lower incidence of hyperthyroid serum TSH values (13, 14). Wilson *et al.* (12) have used a deprivation score as SEP indicator to evaluate the association between TSH and SEP. Similarly, they showed that subclinical hyperthyroidism is positively associated with higher deprivation score values. However, subclinical hypothyroidism was more common in participants with the lowest deprivation score. Probably the relative effect of income and education decreased when combining the SEP indicators with other domains, for example, employment or overall health (12).

It has been hypothesised that individuals with low SEP in general show stronger genetic effects on health than individuals with high SEP. Johnson *et al.* (40) reported that the variance in physical health explained by genetic factors decreases with increasing income in a twin study. Individuals with low SEP are exposed to more health-related risk factors, for example, greater exposure to stress, stronger exposure and vulnerability to behavioural risk factors, and have a higher prevalence of different diseases (41, 42, 43, 44, 45). There are indications that adverse environmental factors may interact with genetic factors

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and influence gene expression through epigenetic modifications (46, 47). A possible explanation could be that genes for disease susceptibility can magnify their effect in a disadvantaged environment with higher rates of risk factors (48). This effect was also detected in studies assessing the association between genetic factors, SEP and BMI, coronary artery calcification or incidence of coronary events (49, 50). However, the interaction between genetic factors and SEP on TSH values in the present study pointed in the opposite direction, as stronger genetic effects were observed in groups of higher SEP. There is an alternative explanation for gene by SEP interactions that hypothesised that individuals with high SEP are exposed to less non-genetic risk factors, which leads to an increased genetic effect in groups of high SEP due to a decrease in the effect of non-genetic factors (51). A Danish study investigated the gene–environment interaction by reference to childcare, SEP and problem behaviour in children. They detected a lower heritability of problem behaviour in children with lower SEP. Likewise, decrease in heritability was explained by an increase in the influence of the environment (52). Further, Ge *et al.* (53) showed that heritability of education increased with increasing SEP. Notably, these studies investigated the effect on heritability, but their results revealed the same direction of interactions as in the present findings. Interestingly, previous studies indicated that genes for mathematical skills are more strongly expressed in high SEP groups, while environmental factors are less important (54, 55). In line with these results, the reported direction of interaction may be explained by a stronger effect of genetic factors in high-education groups, which may present with lower rates of TSH-related non-genetic risk factors.

However, as the overall impact of environmental factors on thyroid dysfunction is largely unknown, there may also be unknown environmental risk factors for thyroid dysfunction which are more prevalent in high education groups. These unknown environmental factors could influence gene expression leading to a stronger genetic effect on TSH values. For instance, several recent studies detected an association between moderate alcohol consumption and lower risk of developing hypo- or hyperthyroidism (14, 56). It is well known that people in high SEP groups are more often moderate drinkers (57). Alcohol and its metabolites play an important epigenetic role in gene expression in neurons through histone acetylation, suggesting a possible influence on gene expression of TSH as well (58, 59). Further, regular physical activity may reduce the risk of developing hypothyroidism, while obesity may be a risk factor for hypothyroidism (14). There are indications that people in high SEP groups are more physically active in their leisure time, while obesity is more frequent in people with low SEP position (60, 61). Further research is required to investigate potential environmental risk factors and their influence on gene expression of TSH-associated genetic loci.

Even further, sensitivity analyses considering only participants without thyroid dysfunction and without thyroid medication did not change the strength and direction of the observed interaction between TSH-related genetic factors and SEP, suggesting that the observed interaction is not mainly triggered by clinical relevant thyroid dysfunction.

Strengths and limitations

The strengths of the present study are its population-based study design and the inclusion of two different SEP indicators. All serum TSH values were measured standardised by the same laboratory with the same immunoassay. The interaction between genetic and socioeconomic factors was not only explored by interaction terms. Stratified analyses and analyses of single reference joint effects supported the main result.

A limitation is the sample size and the limited statistical power for single SNP analyses. Further, time at blood sampling was not standardised, but the secretion of TSH is related to a circadian rhythm showing higher values in the morning and a decrease at noon (62).

Conclusion

To our knowledge, the present study is the first study to explore the interaction between SEP and a genetic effect allele score on TSH. The results gave some weak indication for a modification of the TSH-related genetic effect by education in a population-based study showing stronger genetic effects in groups of high education. Higher SEP groups might be less exposed to non-genetic risk factors so the genetic effect has a stronger impact. Further research is needed to understand the complex relationship between genetic environmental factors and TSH.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0127.

Declaration of interest

None of the authors has a relevant conflict of interest.

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Data availability statement
Due to data security reasons (i.e. data contain potentially participant identifying information), the Heinz Nixdorf Recall Study does not allow sharing data as a public use file. However, others can access the data used upon request, which is the same way the authors of the present paper obtained the data. Data requests can be addressed to: recall@uk-essen.de.

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