# Genetic and environmental determinants of cardiometabolic health

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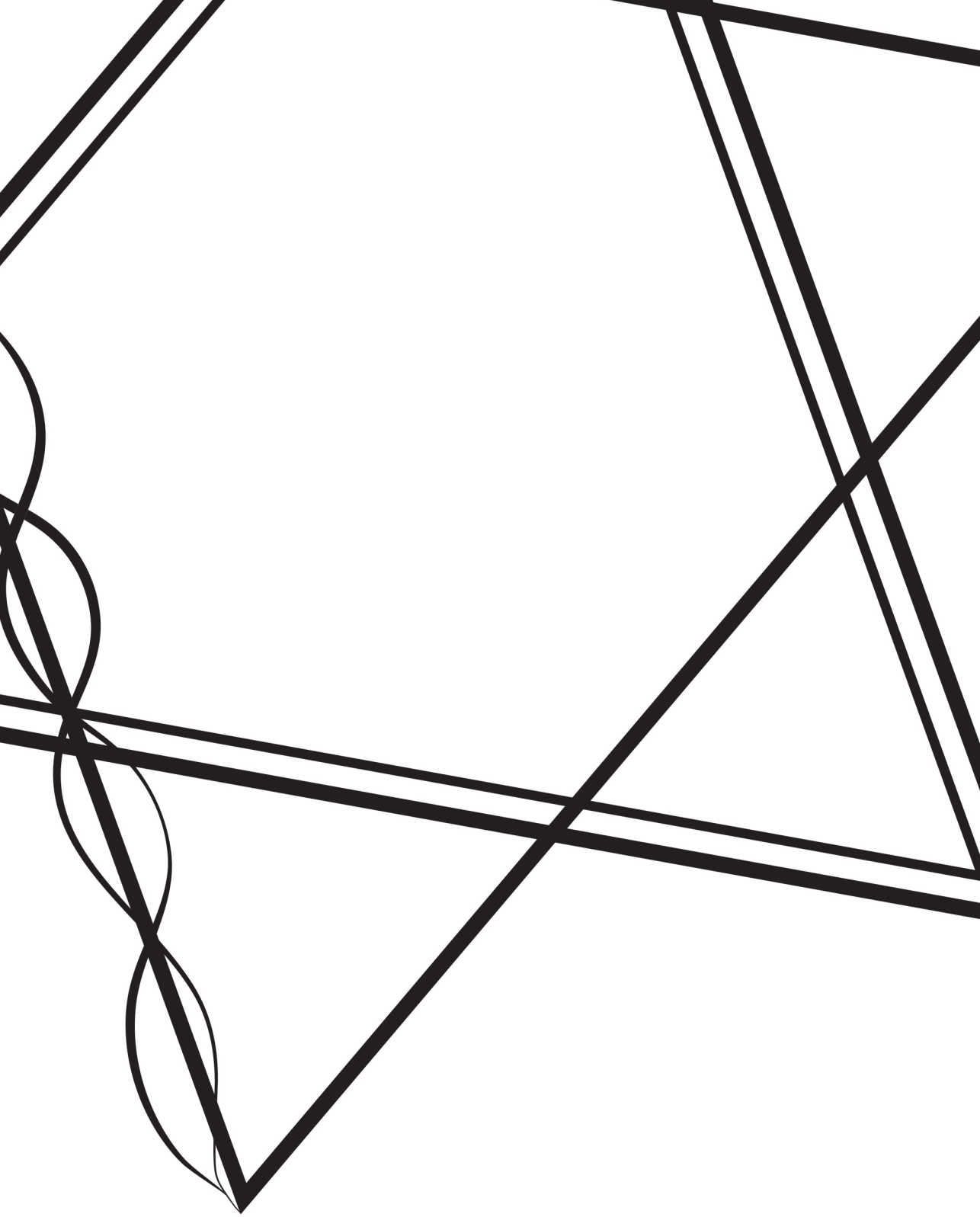

# CHAPTER 5.2

## Genetically-determined higher TSH is associated with lower diabetes mellitus risk in individuals with low BMI: results from the UK Biobank

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*Submitted*

## ABSTRACT

Thyroid status is hypothesized to be causally related with the risk of diabetes mellitus (DM), but previous results were conflicting possibly due to a complex interaction between TSH, BMI and diabetes. In this study, we aimed to investigate the causal association between thyroid status with DM and glucose homeostasis and to what extent this association is dependent on BMI. This study was performed in British participants from the UK Biobank population. Genetic variants for circulatory TSH and fT4 levels and for BMI were used to calculate weighted genetic risk scores (GRS). We assessed the associations between genetically-determined TSH and fT4 and self-reported DM, and stratified the analyses by BMI. Similar analyses were performed on fasting glucose and Hb1Ac as outcomes among individuals without DM. The present study was performed in 401,773 British participants (mean age of 57.4 years (standard deviation 8.0) of which 45.9% were men), of which 19,773 individuals classified themselves as DM cases. Genetically-determined TSH and fT4 levels were not associated with risk of DM in the total UK Biobank population (odds ratio (OR) 0.96; 95% confidence interval (CI) 0.92,1.01). However, we did observe an interaction between genetically-determined TSH and BMI ($p = 0.06$) in their association with DM. In individuals with a low genetically-determined BMI, genetically-determined higher TSH, and not fT4, was associated with a lower risk for DM (OR 0.91; 95%CI 0.85,0.98). A higher genetically-determined TSH was associated with a lower level of fasting glucose and glycated haemoglobin in the overall population and in the groups stratified based on BMI. Genetically determined fT4 was not associated with fasting glucose or glycated haemoglobin. We found evidence for a potential causal association between higher circulatory TSH, but not fT4, and risk for DM. However, only in those with a lower BMI, suggesting protective effects of TSH only in low-risk populations.

# INTRODUCTION

Diabetes mellitus (DM) is a major public health challenge, mainly due to increased prevalence of obesity[1,2]. DM is a heterogeneous disease which is caused by different mechanisms, notably, insulin resistance in muscle, adipose tissue, and liver, and impaired pancreatic insulin secretion[2].

Obesity is a major risk factor of DM development[3]. However, another potential risk factor for DM development is thyroid status, defined by the combined levels of thyroid-stimulating hormone (TSH) and free thyroxine (fT4)[4]. In observational studies, increasing evidence suggests an association between circulating levels of TSH and fT4 with DM[5-8]. However, not all studies support evidence for this association[9].

Moreover, obesity is associated with higher levels of TSH, though the direction of causation is still unclear[10]. Therefore, this complex relation between obesity, thyroid status and DM further complicates studies on causal inference regarding associations between thyroid status and DM. Not all confounder and causal factors are known and/or measured in observational studies and thus it remains unclear whether, and to what extent, thyroid status affects risk of developing DM and how obesity modifies this effect. In a previous study, we used genetic instrument to ascertain causality for associations of circulating levels of TSH and fT4 with DM, but did not find evidence for causality[11]. However, our previous study suffered from some limitations related to the small sample size and lack of (strong) genetic instruments, especially for fT4.



Now, with more than double the number of genetic instruments for TSH and more than quadruple number of genetic variants for fT4 combined with the availability of large sample size individual participant data in UK Biobank, we can readdress this research question in a more rigorous manner. Moreover, in order to study the effect of thyroid status on DM, possible effect modification by body mass index (BMI) should be considered. We hypothesize that obesity has a catalysing effect on the development of DM, especially type 2 diabetes, and could thereby overshadow more subtle causal pathways. By stratification on genetically determined BMI, differential effects of thyroid status on DM can be assessed.

Within the current study, we aimed to investigate the association between thyroid status and glucose homeostasis and the risk of DM in British participants from the UK Biobank. In addition, we stratified our analyses based on genetically-determined BMI in order to test our hypothesis of a possible effect modification by obesity on the association between thyroid status and DM and glucose homeostasis.

# METHODS

*Study population*

For the present study, we included all participants from the UK Biobank with imputed genotype data and self-reported data on DM diagnosis. Between 2006 and 2011, men and women aged 40 till 69 years living within a reasonable travelling distance of one of the 22 assessment centres in the United Kingdom, were invited to participate in the UK Biobank via a population-based register [12]. During their visits to the assessment centres, participants completed questionnaires using a touchscreen device regarding current health and medical history. Body Mass Index (BMI) was established by dividing the weight in kilograms by the height in metres squared. Participants were asked to remove shoes and heavy clothing before weighing [13]. The UK Biobank operates within the terms of an Ethics and Governance Framework and all participants provided signed written informed consent [13,14].

*Genotyping and genetic imputations*

UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axium array for approximately 50,000 participants; the remaining participants were genotyped using the Affymetrix UK Biobank Axiom array. Quality control was centrally executed by UK Biobank. More information on the genotyping processes can be found online (https://www.ukbiobank.ac.uk). Based on the genotyped SNPs, UK Biobank resources performed centralized imputations on the autosomal SNPs using the UK10K haplotype [15], 1000 Genomes Phase 3 [16], and Haplotype Reference Consortium (HRC) reference panels [17]. Autosomal SNPs were pre-phased using SHAPEIT3 and imputed using IMPUTE4. In total, ~96 million SNPs were imputed. Related individuals were identified by estimating kinship coefficients for all pairs of samples using only markers weakly informative of ancestral background.

*Selection of single nucleotide polymorphisms associated with TSH, fT4 and BMI*

For this study, we selected genetic instruments from published genome-wide association studies, in which the UK Biobank did not contribute. For thyroid status, we selected the lead single nucleotide polymorphisms (SNPs) for all genetic loci that have been shown to independently associate with the circulating levels of TSH (42 loci) or fT4 (21 loci) ($P < 5 \times 10^{-8}$) as genetic instrumental variables for TSH and fT4 levels, respectively[18]. To investigate the combined effect of the thyroid hormone associated risk variants, we calculated a weighted genetic risk score (GRS) for circulating TSH or fT4. For the TSH GRS, we excluded rs13100823 in IGF2BP2 as this locus has been associated with type 2 diabetes mellitus[18]. For the fT4 GRS, we excluded rs11039355 in FNBP4 because of its previous association with body height, body mass index and proinsulin[18]. In addition,

we calculated a weighted genetic risk score (GRS) for BMI, for which we selected the lead SNPs for 97 BMI-associated loci [19]. For the present study, we considered a low and high genetically-determined BMI, which was defined on the basis of the median value in the study population.

*Outcome definition*

To define cases with diabetes mellitus, the baseline self-reported interview data collected in the full UK Biobank population was used. All participants reporting to have diabetes mellitus. Moreover, the individuals were asked about the age of diagnosis and whether they used insulin within the first year after diagnosis. Based on the age of diagnosis and use of insulin, we subdivided the self-reported DM diagnosis to homogenize the outcome population. These subdivisions were based on the median age of diagnosis (low/high) and use of insulin (yes/no).

*Statistical analysis*

Characteristics of the study population were expressed as mean with standard deviation for normally distributed measures, and proportions for categorical variables.

We performed multivariable logistic regression analyses to assess the association between the GRSs and DM (subtypes) and linear regression analyses were performed for the associations between the GRSs and the continuous variables glucose and glycated haemoglobin (HbA1C) adjusted for age, sex and four principal components. The resulting estimate is a weighted mean estimate and reflects a standard deviation increase of genetically determined TSH or fT4 on an odds ratio or standard deviation increase of our study outcome. All analyses were adjusted for age, sex and population stratification (first four principal components). To investigate possible effect modification by BMI, our analyses were additionally stratified based on the median of the GRS for BMI. We choose to use a genetically-determined BMI instead of the observational data, in order to minimize the possible effect of reverse causation, treatment and to study life-long exposure to high BMI. In order to formally test for interaction of the GRSs with BMI, we added an interaction term between the thyroid GRS and BMI GRS in their association with DM to the regression models.

In addition, we performed exploratory analyses in which we homogenized the self-reported DM phenotype by age of diagnosis and insulin use. For this, similar multivariable logistic regression analyses were performed as before using a subset of the case groups.

All statistical analyses were performed using R statistical software version 3.5.3. Results were reported as odds ratios (for dichotomous outcomes) or beta estimates (for glucose and Hb1Ac) with 95% confidence intervals.

# RESULTS

*Population characteristics*

After excluding individuals lacking genetic information or those who were of non-European ancestry, this study comprised 401,773 participants with a mean age of 57.4 years (standard deviation 8.0) of which 45.9% were men. A total of 19,773 individuals (4.9%) reported a diagnosis of DM. The population characteristics of the study population are shown in **Table 1** for non-DM cases and DM cases. As compared to controls, DM cases had a higher mean age (57.3 [8.0] versus 60.6 [6.9] years), were more often male (54.1% versus 61.8%), had a higher mean BMI (27.2 [4.6] versus 31.5 [5.8] kg/m$^2$), had a higher fasting glucose (5.0 [0.8] versus 7.6 [3.4] mmol/L) and a higher HbA1c (35.1 [4.5] versus 52.4 [13.7] %).

**Table 1.** Characteristics of study population.

| | No DM (n=389,122) | DM (n=19,773) |
|---|---|---|
| Age at study visit in years | 57.3 (8.0) | 60.6 (6.9) |
| Age at diagnosis in years | - | 50.3 (14.7) |
| Sex, N (% male) | 54.1 | 61.8 |
| BMI in kg/m$^2$ | 27.2 (4.6) | 31.5 (5.8) |
| Fasting glucose in mmol/L | 5.0 (0.8) | 7.6 (3.4) |
| HbA1c in % | 35.1 (4.5) | 52.4 (13.7) |

Data presented as mean with standard deviation or as stated otherwise. Abbreviations: BMI, body mass index; DM, diabetes mellitus; N, number.

*Genetically determined TSH and fT4 with DM*

A genetically-determined higher TSH did not associate with DM in the overall group (odds ratio (OR) 0.96; 95% confidence interval (CI) 0.92,1.01) (**Figure 1**). In the subgroup with a propensity for low BMI (GRS BMI lower than median), a higher GRS for TSH was associated with a lower risk for DM (OR 0.91; 95%CI 0.85,0.98) (**Figure 1**). However, no associations between genetically-determined fT4 and DM were observed in the main group (OR 0.96; 95%CI 0.90,1.03) and in the group with low (OR 0.95; 95%CI 0.84,1.05) and high genetically-determined BMI (OR 0.99; 95%CI 0.90,1.08). We did find suggestive evidence for an interaction between the genetically-determined TSH and genetically-determined BMI on DM (p-value for interaction: 0.06), however, we did not observe a formal interaction for genetically-determined fT4 and genetically-determined BMI on DM (p-value for interaction: 0.19).

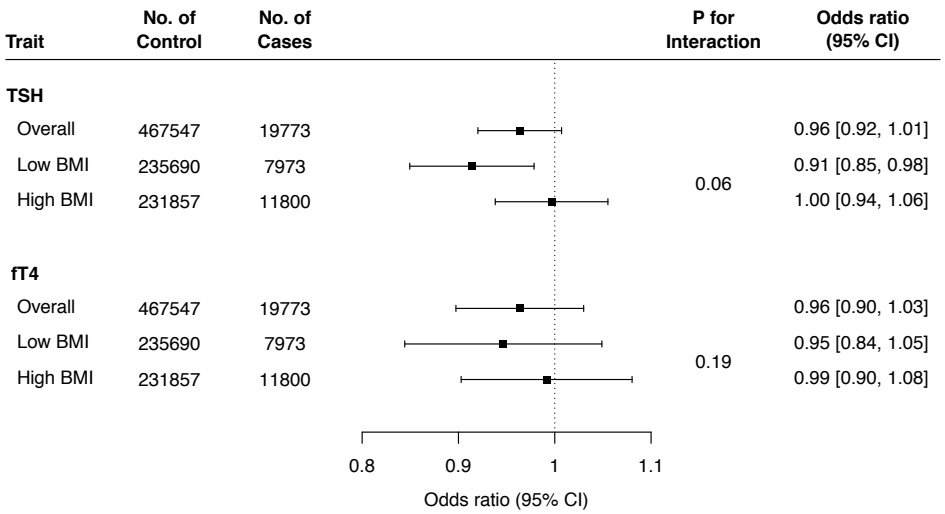


**Figure 1.** *Associations between the GRS for TSH and fT4 with diabetes mellitus in the overall population and stratified by genetically-determined BMI.*

*Genetically determined TSH and fT4 with fasting glucose and glycated haemoglobin*

A higher genetically-determined TSH was associated with a lower level of fasting glucose (beta -0.02; 95%CI -0.03,-0.01) in individuals without DM (**Table 2**). Moreover, a SD higher genetically-determined TSH was associated with lower fasting glucose levels (beta -0.02 mmol/L; 95%CI -0.03,-0.01)), in the group of individuals with a low BMI as well as in the group of individuals with a high BMI (beta -0.02 mmol/L; 95%CI -0.00,-0.03)(**Table 2**). The results for the GRS of TSH on glycated haemoglobin showed a similar trend, although with wider confidence intervals. Genetically determined fT4 was not associated with fasting glucose or glycated haemoglobin.



**Table 2:** *Associations between the GRS for TSH and fT4 with fasting glucose and HbA1c, stratified by genetically-determined BMI.*

| | | | Low BMI | | High BMI | |
|---|---|---|---|---|---|---|
| | TSH | T4 | TSH | T4 | TSH | T4 |
| Fasting glucose | -0.02 (-0.03;-0.01) | -0.00 (-0.01;0.01) | -0.02 (-0.03;-0.01) | 0.00 (-0.01;0.02) | -0.02 (-0.03;-0.00) | -0.00 (-0.02;0.01) |
| HbA1c | -0.03 (-0.07;0.02) | 0.02 (-0.05;0.09) | -0.01 (-0.07;0.06) | -0.00 (-0.10;0.10) | -0.05 (-0.11;0.01) | 0.05 (-0.04;0.15) |

Data presented as SD increase in GRS per SD difference in outcome with accompanying 95% confidence interval. A total of 467,547 individuals are included in the overall analyses, 231,857 in the low BMI group and 235,690 in the high BMI group.

*Sensitivity analyses in DM subtypes*

In sub-analyses of this study, we also explored the associations in DM subgroups based on initiation of treatment with insulin (analogues) within the first year after diagnosis and on the age at diagnosis. Here we did observe an association between a higher GRS for TSH and a lower risk for DM diagnosed at a younger age for which patients did not require insulin(analogues) within the first year for those with a low BMI (OR 0.87; 95%CI 0.77, 0.98) (**Figure 2**).

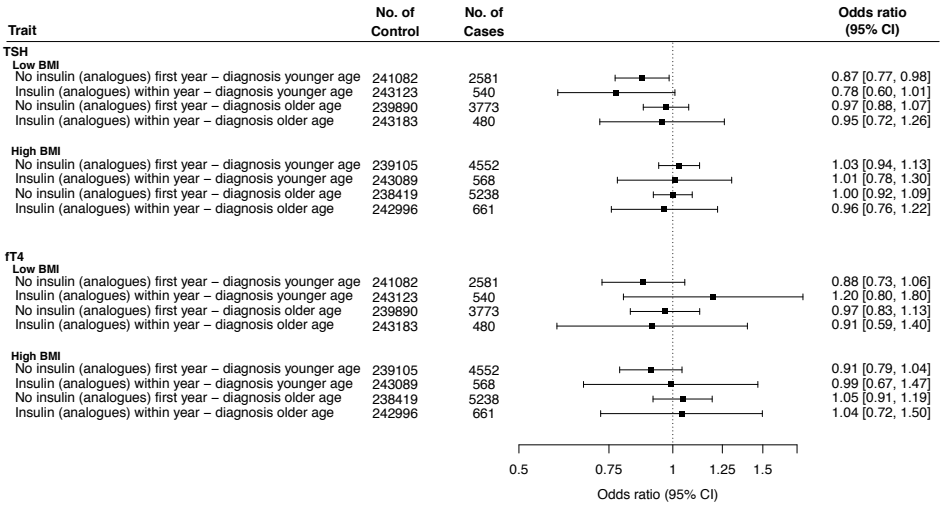


**Figure 2.** *Associations between the GRS for TSH and fT4 with subgroups of diabetes mellitus stratified by genetically-determined BMI.*

# DISCUSSION

In this study, we examined the associations between genetic-risk scores for circulating TSH and fT4 levels with DM and glucose homeostasis. In the total British UK Biobank population, we did not find evidence for an association between genetically-determined TSH or fT4 with DM. However, when stratified based on genetically-determined BMI, higher genetically-determined TSH was associated with a lower risk of DM in the group with a low genetically-determined BMI. Moreover, higher genetically-determined TSH was associated with a lower fasting glucose level, in the overall group and those stratified based on genetically-determined BMI. Though no associations were found between genetically-determined fT4 and any of our study outcomes.

A strength of this study is the use of a large sample size with a large number of DM cases, which allowed for stratified analyses based on genetically-determined BMI and exploratory analyses on DM subgroups. By stratification on genetically determined BMI, the hypothesized catalysing role of obesity was taken out of the equation, revealing the more subtle causal pathway of the HPT-axis on DM. Certain limitations of this study also need to be addressed. The present study made use of self-reported touchscreen based data, which might be prone to measurement error. As measurement error is likely to be unrelated to the genetic factors (e.g., nondifferential misclassification) this likely resulted in a reduced statistical power. Furthermore, because the genetic instrumental variables, as well as the outcome data set, originated from populations of European ancestry, our results may not be generalized to populations of non-European ancestry.



The findings of the current study add to previous research regarding the role of low thyroid status and DM onset. Several observational human studies observed an association of higher TSH level with a higher risk of DM[6-8]. However, not all observational studies showed an association between higher TSH and DM. De Vries et al. (2019) did not observe a relation between plasma TSH levels within the normal range and incident DM in patients at high cardiovascular risk[9]. The lack of a causal association with TSH and fT4 as observed in the overall study population of the current study may suggest that previously observed associations of alterations in thyroid status and DM onset might have resulted from reverse causality and/or residual confounding. One of the potential interfering mechanisms could be central resistance to thyroid hormones commonly seen coinciding with metabolic syndrome[20]. In addition, many other factors such as auto-immune disorders, could cause residual confounding. Furthermore, these findings confirm our previous observations of no association between circulating TSH and fT4 and risk of DM at population level using two-sample Mendelian Randomization analyses with fewer instruments in a smaller study population[11].

The main novel observation of the current study is the association of higher genetically determined circulating TSH levels with a lower risk of DM in individuals with a lower genetically-determined BMI. Two main routes of action can be hypothesized; either a direct effect of TSH or an indirect route via a lower HPT-axis setpoint. For TSH to have a direct effect on tissue function, TSH-receptors (TSHRs) are required. Various extrathyroidal expression of TSH-receptors are described in literature, including in orbital fibroblasts, adipose tissue, bone, skeletal muscle, thymus and kidney[21,22]. TSH could exert its protective effect against DM via adipose tissue. In mice and human adipocytes expression of TSHR was demonstrated previously [23,24]. Adipocytes were also shown to increase lipolysis in response to stimulation with TSH *in vitro* and *in vivo* [23,24]. Furthermore, interaction with the insulin signaling pathway was demonstrated, leading to an inhibition of PI3K resulting in lower rates of adipogenesis [25]. Thus, higher levels of TSH could potentially be protective against accumulation of adipose tissue and thereby reduce the risk of DM. Alternatively, TSH could influence glucose homeostasis through increasing insulin sensitivity and glucose uptake of skeletal muscle. In line, we described a causal association between higher TSH levels and lower fasting glucose levels in this study. Moon *et al*. (2016) have demonstrated a direct stimulatory effect of TSH on insulin receptor substrate (ISR)-1 expression in muscle tissue and improved glucose tolerance[26]. Another potential etiological pathway could be via immunomodulation. TSHR was shown to be present in thymus tissue, and stimulation with TSH increased development and differentiation of T-cells in both rodent and human thymal cell lines[27]. Hence, individuals with higher circulating levels of TSH could be having a more diverse and effective adaptive immune system. Having a diverse arsenal of T-cells prevents auto-immunity and other sources of low-grade inflammation[28]. As low-grade inflammation is a well-established causal risk factor for developing DM, any factor targeting inflammatory pathways could be a potential strategy for prevention of DM [29]. Higher TSH levels could be such an immunomodulating factor protecting against DM. Apart from direct effects of TSH, an indirect effect of higher TSH via a different HPT-axis setpoint could also explain our findings. As expected from the strong inverse relationship between TSH and fT4, virtually all genetic variants for higher TSH are associated with lower circulating levels of fT4 in the original GWAS[18]. Therefore, our observation could be elaborated to an association of higher TSH and lower fT4, i.e. a lower HPT-axis setpoint, with a lower risk of DM. Previously, thyroid status has been linked to multiple components of glucose homeostasis. It has long been known that thyroid hormones induce hepatic gluconeogenesis[30]. Furthermore, thyroid hormones could affect insulin production and secretion in the pancreas[31]. Although thyroid hormones are required for maturation of pancreatic β-cells, senescence is also accelerated by elevated levels of thyroid hormones in these insulin producing cells [32].

Here, we specifically studied the effects of circulatory TSH and fT4 on DM onset and glucose homeostasis. However, target tissues customize intracellular thyroid hormone levels to their current needs independently of circulating levels in the blood[33]. Deiodinases are key players in the modulation of the availability of thyroid hormones in target tissues [34]. In previous research of our group, we demonstrated that genetic variation in *DIO1* may affect glucose metabolism [11]. This may be more reflective of target tissue levels of thyroid hormone than the circulating levels. We therefore propose that future studies should focus on the role of deiodinases and availability of thyroid hormones in target tissues on glucose homeostasis and the risk of DM.

# CONCLUSION

In this study, genetically-determined circulating TSH was associated with a lower risk of DM in participants with low genetically-determined BMI. Moreover, a higher genetically-determined TSH is associated with lower fasting glucose levels in participants without DM, in the overall population and in individuals with both low and high genetically-determined BMI. We did not find evidence for a causal association between higher circulatory TSH or fT4 levels and any of our study outcomes. These findings may indicate that TSH levels affect glucose homeostasis and that higher TSH levels might protect against DM. Only finding these associations in subgroups at lower risk may indicate a more subtle role of the HPT-axis in the aetiology of DM.

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**Duality of interest**
The authors declare to have no conflict of interest.

**Contribution statement**
Concept and study design: MMB, NAvV, SPM, RN, DvH. Data analyses: MMB, NAvV. Drafting the initial versions of the manuscript: MMB, NAvV. Data collection: RN. Supervision: RN, DvH. Commenting on draft versions of the manuscript: RN, SPM, DvH. Final approval of the manuscript: MMB, NAvV, SPM, RN, DvH.

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