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Sex hormone-binding globulin and sex-specific association between irritable bowel syndrome and type 2 diabetes: a prospective cohort study

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Abstract

Objective To investigate the sex-specific association between irritable bowel syndrome (IBS) and type 2 diabetes (T2D), and further explore whether sex-hormone binding globulin (SHBG) was an associated factor of the sex-specific association.

Methods The study was a prospective analysis based on the UK biobank (UKB) data. We included 359 503 participants, all of whom were without diabetes diagnosis and had complete SHBG information at baseline. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using non-IBS group as the reference, further stratified by sex and SHBG levels in multivariable-adjusted models, including demographics, lifestyle factors, and disease history.

Results During a median follow-up of 10.4 years, 14 317 incident T2D cases had been documented. A statistically significant increased risk of T2D with IBS compared to those without IBS was observed in all multivariable-adjusted models (HR = 1.32, 95% CI = 1.23–1.42, $P < 0.001$). Additionally, a sex-specific association between IBS and T2D was found ($P_{interaction} = 0.004$), with the risk in women (HR = 1.43, 95% CI = 1.31–1.57) being higher than in men (HR = 1.14, 95% CI = 1.01–1.29). A significant effect modification of SHBG was also observed in the association between IBS and T2D ($P_{interaction} = 0.001$). The risk of incident T2D was higher in participants with higher SHBG levels (HR = 1.42, 95% CI = 1.25–1.63) than in those with lower SHBG levels (HR = 1.26, 95% CI = 1.16–1.37).

Conclusions A sex-specific association between prevalent IBS and T2D incidence was found, and SHBG level might modify the association.

Keywords Irritable bowel syndrome, Type 2 diabetes, Prospective cohort, Stratified association

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Introduction

Irritable bowel syndrome (IBS) is one of the world's most common disorders of gut-brain interaction, presenting with long-term recurrent abdominal pain accompanied by changes in bowel habits, but with no organic disease detected [1]. The global prevalence of IBS was 11.2% [2], affecting individuals' quality of life and imposing a considerable health and economic burden on society [3]. During the Coronavirus disease 2019 (COVID-19) pandemic, IBS patients in tertiary care had a higher symptom burden than before COVID-19 [4], strengthening the importance of preventing the disease. Diabetes is a major global health problem, and 536.6 million people had diabetes in 2021 [5]. The prevalence of diabetes is projected to be 12.2% in 2045 worldwide [5]. IBS patients are more likely to develop T2D [6], and might be positively correlated with higher fasting glucose levels [7]. In a case–control study, prevalence of pre-diabetes of patients with IBS was higher compared to the controls [8]. Lately, a potential pathway linking T2D and IBS has been discovered. For example, *R. gnavus* and its-derived tryptamine and phenethylamine, might have a positive correlation with insulin resistance in patients with IBS [9].

Notably, the prevalence of IBS in women (14.0%) was higher than that for men (8.9%) [2], but the mechanism behind it is still yet to be found [10–12]. Moreover, a study based on data from the National Health Insurance Research Database in Taiwan, 2011–2018 [13], also found that the incidence of IBS for women was higher than for men. However, though the sex-related differences in the two diseases both exist, there still lacks studies focusing on the sex-specific differences in the association between IBS and T2D.

Sex hormone-binding globulin (SHBG) is a glycoprotein that is synthesized primarily in the liver, playing a crucial role in regulating the bioavailability of sex steroids, including estrogen and testosterone by binding to them. Because it could influence adiposity and metabolic functions by regulating the concentration of bioavailable sex hormones, SHBG has already been used as a sex-stratified factor in studying the body fat percentage in genome-wide association studies (GWAS) using UK Biobank (UKB) data [14]. Of note, rising evidence shows that SHBG might have a relation with insulin resistance, then further influences the progress of T2D [15, 16]. Several epidemiological studies have shown that lower SHBG is an independent risk factor of T2D [17–19]. In addition, the association between SHBG and T2D seems to be stronger in women than men [19].

Hence, based on the hypothesis that IBS may contribute to a higher risk of T2D [6, 8], this study aims to find the potential sex-specific association between IBS and T2D using data from the UKB, and further investigate whether the sex-specific association is caused by SHBG levels.

Study design and population

This study was a prospective analysis based on the UKB. A detailed description of the study design was reported previously [20]. Briefly, over 500,000 participants aged between 37 and 73 years were enrolled in 22 assessment centers across England, Wales, and Scotland between 2006 and 2010. All participants provided information through touch-screen questionnaire data, physical measurements, and blood and urine samples. The UKB was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382), and all participants signed written informed consent. This research was conducted using the UKB resources under application 66,137.

We excluded 26 741 participants with prevalent diabetes diagnosis, 7524 with celiac disease or inflammatory bowel disease diagnosis, 44,581 with any cancer diagnosis at baseline. In addition, 64,073 participants whose SHBG information was missing were also excluded, leaving 359 503 participants included in the final analysis. And the definition of was acquired from central registry at recruitment, updated by self-reported sex.

Definition of irritable bowel syndrome

UKB used first occurrences data to define prevalent and incident cases. First occurrences information was derived from linkage to primary care or hospital admission data as well as self-reports. IBS diagnosis was confirmed using International Classification of Disease-10 (ICD-10) code of K58. IBS cases were only identified and classified at the study baseline. Participants with first-reported diagnosis date prior to baseline survey time were considered as the prevalent IBS group, whereas the others were in the non-IBS group [21, 22].

Ascertainment of type 2 diabetes

Incident T2D cases were identified when the diagnosis time of individuals with T2D were after the baseline survey date. T2D status was also determined by first occurrences data with ICD-10 code of E11 [23, 24].

Assessment of sex hormone-binding globulin

Serum SHBG concentrations (nmol/L) were measured by Beckman Coulter DXI 800 on the Beckman Coulter (UK), Ltd using blood sample collected at baseline survey. The detailed information of calibration and quality control process on the measurement is provided at the UKB website (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/serum_biochemistry.pdf). The coefficients of variation of SHBG for the samples with low, medium, and high levels

of internal quality control were 5.22%, 5.25%, and 5.67%, respectively. In addition, the external quality assurance result for SHBG was 95%.

Covariates

Potential confounders, namely sociodemographic characteristics, lifestyle behaviors, and comorbidities at baseline were all adjusted when examining the association between IBS and T2D. Sociodemographic characteristics included age (continuous, years), sex (men/women), ethnicity (white European, mixed, South Asian, black, others), Townsend Deprivation index (continuous). Townsend Deprivation index was calculated immediately prior to participants joining in UKB using indicators of unemployment, non-home ownership, non-car ownership, and household overcrowding. A higher Townsend Deprivation index represents a higher level of deprivation [25]. Lifestyle behaviors included smoking status (never, current or former), alcohol drinking (never, current, or former), physical activity (continuous, MET-minutes), healthy diet score (0, 1, 2, 3, 4, 5), and body mass index (BMI, continuous, kg/m^2). Physical activity was classified into low, moderate, and high levels based on the International Physical Activity Questionnaire. The healthy diet score was calculated using five components: vegetables, fruit, fish, processed meat, and unprocessed red meat. Each one point was given for each favorable diet factor, with the healthy diet score ranging from 0 to 5 [26]. Comorbidities included hypertension (yes/no), cardiovascular disease (yes/no), cholesterol levels (continuous, mmol/L), family history of diabetes (yes/no), and menopause status (yes/no, women only). The history of prevalent hypertension and cardiovascular disease was determined from self-reported information and medical records. Additionally, serum cholesterol levels were measured using the enzymatic method (Beckman Coulter (UK), Ltd). The family history of T2D was defined by an illness history of first-order relatives.

Statistical analysis

Baseline characteristics were described by mean for continuous variables and percentage for categorical variables. The Cox proportional hazard model was adopted to examine the sex-specific association between IBS and T2D. Hazard ratio (*HR*) and 95% confidence interval (*CI*) were calculated using non-IBS group as the reference. The follow-up period was defined from baseline survey time to the date of T2D diagnosis, death, or the latest time of available data (31 July 2019), which came first. For missing data, mean values were imputed for continuous variables and missing indicators were used for categorical variables. The missing rates of the covariates were: race (0.45%), Townsend index (0.12%), drinking status (0.24%), smoking status (0.48%), physical activities (18.90%), healthy diet score (4.29%), serum cholesterol levels (0.06%), BMI (0.33%), and family history of diabetes (22.44%). Proportional hazard assumption was ascertained by Schoenfeld residuals method.

Three adjustment models were conducted: (1) model 1 adjusted for demographics including age, UKB assessment center, race, and Townsend Deprivation index; (2) model 2 further adjusted for alcohol consumption, smoking status, physical activity, healthy diet score, and BMI; and (3) model 3 additionally adjusted for hypertension, cardiovascular disease, serum cholesterol levels, family history of diabetes, and menopause status (women only). Subgroup analysis was further performed to explore whether the association between IBS and T2D differed by sex. Furthermore, effect modification was evaluated by adding a cross-product interaction term of sex and IBS group in all models. To explore whether the association between IBS and T2D was modified by SHBG concentrations, stratified analysis by median SHBG concentrations (< 45.6 nmol/L and ≥ 45.6 nmol/L) was also conducted. Moreover, we performed a mediation analysis, assuming that the SHBG partially mediated the significant association of IBS with T2D. We performed the Cox proportional hazard model analysis separately for IBS and T2D, IBS and SHBG, and SHBG and T2D, to assess how SHBG mediates the occurrence of T2D.

Additionally, several sensitivity analyses were conducted to assess the robustness of the findings. First, we further adjusted for oestradiol and testosterone levels in the models. In addition, T2D cases during 2 years of follow-up were excluded to avoid reverse causality. Moreover, updated information on IBS status was included in the current findings based on the same covariates from baseline.

A 2-tailed P value of <0.05 was defined as statistically significant. All analyses were conducted using SAS software version 9.4.

Results

Table 1 shows the sex-specific characteristics of the study participants at baseline. Men participants were older and had higher Townsend Deprivation index and BMI levels. In addition, men were more likely to be current drinkers and current smokers. They also tended to be physically active and have an unhealthier diet. Furthermore, the prevalence rates of hypertension and CVD of men were higher than women. A significant difference of SHBG by sex existed. Besides, participants with IBS at baseline were less likely to be current drinkers and smokers and were more likely to have a healthy diet. Participants with IBS tended to have lower BMI levels. The prevalence of hypertension in participants with IBS was lower but the

Table 1 Baseline characteristics of participants by sex and by irritable bowel syndrome. Continuous and categorical variables are presented as mean and percentages (%), respectively

	By sex			By irritable bowel syndrome (IBS)		
	Men	Women	*P*	Without IBS	With IBS	*P*
N	167 010	192 493		341,660	17,843	
Sex, women (%)				52.5	72.9	**< 0.001**
Age (years)	56.1	55.9	**< 0.001**	56.0	55.9	**0.009**
Race, white (%)	94.3	94.4	**< 0.001**	94.2	96.4	**< 0.001**
Townsend Deprivation index	−1.3	−1.4	**< 0.001**	−1.3	−1.4	0.089
Current drinkers (%)	93.9	90.9	**< 0.001**	92.4	90.4	**< 0.001**
Current smokers (%)	12.7	8.8	**< 0.001**	10.7	9.9	**0.003**
Physical activity level (%)			**< 0.001**			**< 0.001**
Low	15.7	14.2		14.8	16.2	
Moderate	32.3	33.6		33.4	29.6	
High	36.7	30.2		18.8	21.8	
Healthy diet score			**< 0.001**			**< 0.001**
0–1	17.5	7.4		12.2	10.4	
2–3	53.1	45.5		49.0	47.9	
4–5	29.4	47.2		38.7	41.8	
Body mass index (kg/m^2)	27.6	26.9	**< 0.001**	27.3	27.1	**< 0.001**
Prevalent hypertension (%)	59.7	47.0	**< 0.001**	53.1	48.9	**< 0.001**
Prevalent cardiovascular disease (%)	8.5	3.9	**< 0.001**	6.0	6.2	0.432
Family history of diabetes (%)	19.1	21.6	**< 0.001**	22.5	22.1	**< 0.001**
Cholesterol (mmol/L)	5.6	5.9	**< 0.001**	5.8	5.8	**< 0.001**
Sex hormone binding globulin (nmol/L)	39.6	62.6	**< 0.001**	51.7	55.9	**< 0.001**
Prevalent irritable bowel syndrome (%)	2.89	6.76	**< 0.001**			

prevalence of cardiovascular diseases was higher. Also, SHBG of participants was higher in participants with IBS compared with those without IBS.

During a median follow-up of 10.4 years (3,661,035 person-years), we documented 14 317 incident T2D cases. For both men and women cases, statistically significant increased risks of T2D with IBS compared to those without IBS were observed in all three models (all $P < 0.001$) (Supplementary Table 1). In the first model adjusted for age, sex, UKB assessment center, race, and Townsend Deprivation index, for participants with IBS, the HR for developing T2D is 1.34 (95% CI:1.25–1.43). Similar results were shown in model 2, with additively adjusted for alcohol consumption, smoking status, physical activity, healthy diet score, and BMI. When further adjusted for prevalent hypertension, prevalent CVD, cholesterol levels, and family history of diabetes based on model 2, model 3 presented a slightly lower HR of 1.32 (95% CI: 1.23–1.42).

We further found a sex-specific association between prevalent IBS and T2D incidence in all adjusted models (Table 2). In men, models 1, 2, and 3 showed HRs of 1.15 (95% CI:1.02–1.30), 1.14 (95% CI:1.01–1.29), and 1.14 (95% CI:1.01–1.29), respectively. For women, the HRs were higher across the models: 1.47 (95% CI: 1.35–1.60), 1.48 (95% CI: 1.36–1.62), 1.43 (95% CI: 1.31–1.57), respectively. In addition, the interaction between sex and IBS on incident T2D was also tested in all models, revealing a significant effect modification of sex in the association between IBS and incident T2D ($P_{\text{interaction}} = 0.002$, 0.001, 0.004, respectively).

SHBG level was significantly associated with T2D (HR = 0.981, 95%CI: 0.980–0.982, $P < 0.001$), after adjusting for age, sex, UK Biobank assessment center, race, Townsend Deprivation index, alcohol consumption, smoking status, physical activity, healthy diet score, body mass index, prevalent hypertension, prevalent cardiovascular disease, cholesterol, family history of diabetes, and IBS. A stratified analysis was conducted according to SHBG levels, and significant interactions between SHBG and IBS on the risk of T2D incidence were observed in all models, as Fig. 1 shows. In individuals with higher SHBG levels, IBS was more strongly associated with incident T2D with the HR = 1.43 (95%CI: 1.25–1.63), 1.43 (95%CI: 1.26–1.64), 1.42 (95%CI: 1.25–1.63), respectively in three models. In contrast, for individuals with lower SHBG levels, the HRs were 1.28 (95%CI: 1.17–1.39), 1.28 (95%CI: 1.18–1.39), 1.26 (95%CI: 1.16–1.37), respectively.

Table 2 Sex-specific hazard ratio and 95% confidence interval of irritable bowel syndrome with incident type 2 diabetes

	Men			Women			
	Irritable bowel syndrome			Irritable bowel syndrome			
	No	Yes	*P*	No	Yes	*P*	$P_{interaction}$
Cases/N	8092/162 180	278/4830		5382/179 480	565/13013		
Model 1[a]	1.00	1.15 (1.02–1.30)	0.02	1.00	1.47 (1.35–1.60)	< 0.001	0.002
Model 2[b]	1.00	1.14 (1.01–1.29)	0.03	1.00	1.48 (1.36–1.62)	< 0.001	0.001
Model 3 [c]	1.00	1.14 (1.01–1.29)	0.03	1.00	1.43 (1.31–1.57)	< 0.001	0.004

[a] Adjusted for age (continuous, years), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), and Townsend Deprivation index (continuous)

[b] Adjusted for age (continuous, years), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), Townsend Deprivation index (continuous), alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), physical activity (continuous, MET-minutes), healthy diet score (0, 1, 2, 3, 4, 5), and body mass index (continuous, kg/m^2)

[c] Adjusted for age (continuous, years), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), Townsend Deprivation index (continuous), alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), physical activity (continuous, MET-minutes), healthy diet score (0, 1, 2, 3, 4, 5), and body mass index (continuous, kg/m^2), prevalent hypertension (yes/no), prevalent cardiovascular disease (yes/no), cholesterol (continuous, mmol/L), family history of diabetes (yes, no, or missing), and menopause status (yes/no, women only)

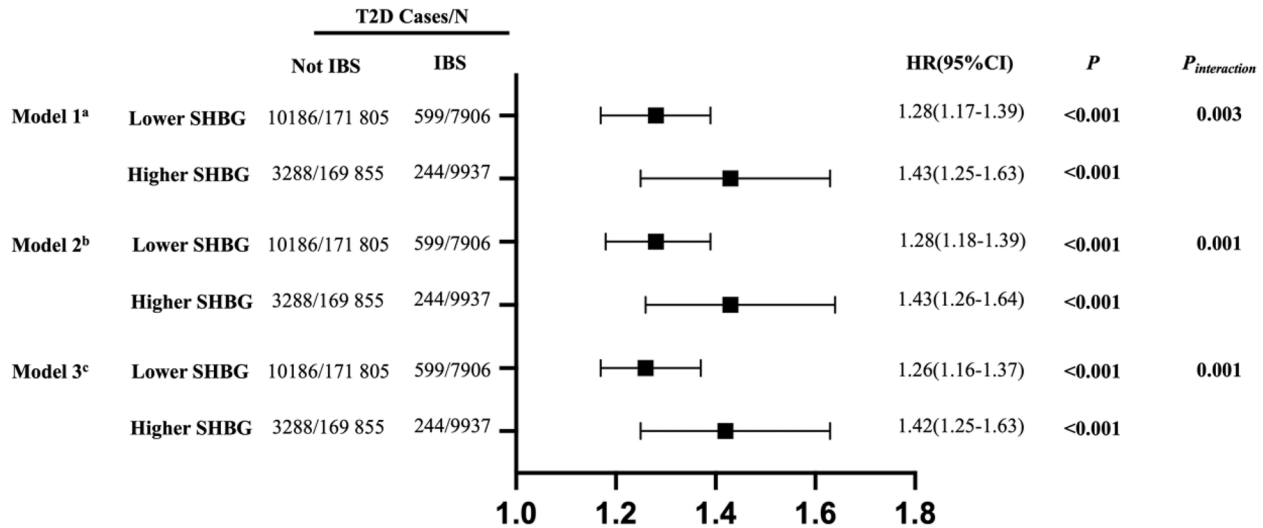

Fig. 1 Hazard ratio and 95% confidence interval of irritable bowel syndrome with incident type 2 diabetes by sex hormone binding globulin groups. [a] Adjusted for age (continuous, years), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), and Townsend Deprivation index (continuous). [b] Adjusted for age (continuous, years), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), Townsend Deprivation index (continuous), alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), physical activity (continuous, MET-minutes), healthy diet score (0, 1, 2, 3, 4, 5), and body mass index (continuous, kg/m^2). [c] Adjusted for age (continuous, years), sex (male/female), UK Biobank assessment center, race (white European, mixed, South Asian, black, others), Townsend Deprivation index (continuous), alcohol consumption (current, former, never, missing), smoking status (current, former, never, missing), physical activity (continuous, MET-minutes), healthy diet score (0, 1, 2, 3, 4, 5), and body mass index (continuous, kg/m^2), prevalent hypertension (yes/no), prevalent cardiovascular disease (yes/no), cholesterol (continuous, mmol/L), and family history of diabetes (yes, no, or missing). $P_{interaction}$: *P* value of the interaction term of IBS and SHBG

Significant interactions of SHBG in the relation between IBS and T2D have been discovered in all participants ($P_{interaction}$ = 0.003, 0.001, 0.001, in three models respectively). In addition, further adjusting for SHBG (HR: 1.15, 95% CI:1.02–1.29 for men and HR: 1.42, 95% CI:1.30–1.55 for women) attenuated the sex difference in the IBS-T2D relationship compared with the model 3. The mediation analysis showed that SHBG (mediation proportion: 3.53%) significantly mediated the association of IBS with T2D (*P* for mediation < 0.001).

We performed sensitivity analyses, showing that the results were essentially unchanged after further adjustment for oestradiol and testosterone levels (Supplementary Table 2), limiting participants with a follow-up time

of more than 2 years (Supplementary Table 3), excluding the participants with missing data of physical activity and family history of T2D (Supplementary Table 4) or including information of updated IBS incidence (Supplementary Table 5).

Discussion

In this large prospective cohort study of the UKB, we mainly found that there was a significant, and sex-specific association between prevalent IBS and incident T2D. Additionally, a significant interaction of SHBG and IBS for T2D was observed, and in participants with higher SHBG levels, the association between IBS and T2D was stronger in all multivariate-adjusted models. As SHBG could be a sex-stratified factor, the results could provide mutual corroboration for the sex-specific association between IBS and T2D.

Some existing studies have suggested a higher prevalence of T2D symptoms among individuals with IBS compared to the general population [8, 9], which supports the results in the current study. The potential mechanisms leading to the higher prevalence of T2D symptoms in IBS patients might relate to insulin resistance, possibly caused by gut microbiota-derived tryptamine and phenethylamine [9]. Besides, dysbiosis [27] is a common feature in both conditions and may represent a shared pathophysiological pathway. Moreover, the gut-brain axis as a bridge linking gut microbiota and brain nerves, has been proven to be involved in the pathology process of IBS and might be devoted to T2D by glucose homeostasis [28]. As for medications, those used to treat T2D which particularly affect gastrointestinal motility, can influence IBS symptoms [29]. Conversely, the management of IBS on certain medications or dietary changes may have implications for blood glucose control in T2D [30].

To the best of our knowledge, it is the first study to assess the interaction of sex and IBS for T2D. The results showed a stronger association between IBS and T2D in women than in men, which exactly matches the findings of previous studies focusing on the sex differences in the risk of IBS [31] and T2D [18, 19], respectively. Additionally, the current study also found that the association between IBS and T2D was stronger in participants with higher SHBG levels than those with lower SHBG levels. As the level of SHBG is higher in women than men, the current results may come down to one possible explanation: SHBG is the potential associated factor of this sex difference between the two diseases.

Scholars have been far working on pathophysiological and epidemiological studies to understand the complex mechanism between SHBG and T2D [9, 32]. One hypothesis is that low SHBG levels may reflect a hormonal environment conducive to insulin resistance [33], a hallmark of T2D. Insulin resistance, in turn, may lead to compensatory hyperinsulinemia, which has been suggested to suppress hepatic SHBG production [33, 34]. Additionally, related to estrogen, SHBG may be involved in the modulation of inflammatory pathways, which are known to contribute to the development of insulin resistance and T2D [35]. Therefore, SHBG may have a direct role in the pathophysiological processes leading to T2D. Also, the sex classification of IBS is to be focused on, a higher prevalence of IBS in women compared to men [31, 36]. First, hormonal differences, particularly the effects of estrogen and progesterone might influence gastrointestinal motility and sensitivity [37]. Fluctuations in these hormones during the menstrual cycle can affect gut function, which might explain the increased prevalence and severity of IBS symptoms in women during certain phases of their menstrual cycle [37, 38]. Also, rising evidence [39] suggests that gut microbiota composition varies between men and women, which might impact the development and manifestations of IBS, but the response toward fecal microbiota transplantation of both sexes turns out to be no difference by a study including 164 IBS patients [40]. Besides, the psychology [38] of different sexes may lead to the difference in IBS reporting and medication, further form the sex classification. Considering both two diseases, SHBG could be the reason why sex differences were observed in their association, possibly related to the sex-specific hormones, insulin resistance and gut microbiota.

Meanwhile, as this study focused on the relationship between IBS cases and incident T2D, it is important to note that treatments for IBS, particularly medications like tricyclic antidepressants, which are commonly used in clinical practice, may associated with T2D risk through mechanisms such as weight gain [41]. These treatments could act as confounders in studies exploring the association between IBS and diabetes, and future research should address the potential impact of IBS medications on T2D risk.

There are some strengths in this current large prospective cohort study. First, three multivariate-adjusted models were conducted to best minimize the possible bias, with sociodemographic, lifestyle and hormonal factors being considered. Second, several sensitivity analyses were conducted, with stable results to validate the robustness of the findings. Third, we observed SHBG significantly mediated the association of IBS with T2D. However, the study has some limitations. First, we could not detect the causal relationship of SHBG levels and IBS with T2D due to the observational design. Second, there is only one detection of SHBG level, more measurements in the future are needed to validate the fluctuation of the association. Third, due to the low response rate to

recruitment invitations from UKB [42], less socioeconomically deprivation might lead to fewer risk factors in long-term diseases of participants, further leading to uncontrolled selection bias. Additionally, the definition of IBS based on the diagnostic code could lead to underdiagnosed IBS patients, further causing a potential misclassification.

Conclusions

In this study, we found individuals with prevalent IBS had a higher risk of incident T2D, in which women are at higher risk than men. SHBG may also modify the relation between IBS and T2D, and it might be one of the associated factors for the sex-specific association between IBS and T2D. In the future, to better understand the sex-specific relationship between IBS and T2D, so as to develop better prevention or medication measures for these diseases, further clinical trials are expected to validate the findings above urgently.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01155-z.

Supplementary Material 1.

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All authors declare no conflict of interest.

Authors' contributions
M.W., T.H., and T.W. made the conception and designed the work; Y.T., H.G., H.P. did the data extraction and statistical analysis; S.W., Y.Z., and T.H. helped with software use in the work; C.G. and W. X. helped the data visualization. M.W. and Y.T. wrote the manuscript draft; T.W. and T.H. made revisions. All authors approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The UKB was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382), and all participants signed written informed consent.

Consent for publication
All participants provided informed consent.

Competing interests
The authors declare no competing interests.

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