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Sex hormone-binding globulin, genetic susceptibility, and the risk of type 2 diabetes in men and postmenopausal women

Wen Zhang, Haojie Zhang, Bin Wang, Yuying Wang, Ningjian Wang, Yingli Lu

Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China.

To the Editor: Type 2 diabetes (T2D) is one of the most common and fastest growing non-communicable diseases worldwide. Sex hormone-binding globulin (SHBG) is a circulating homodimeric glycoprotein that can bind androgens and estrogens with high affinity in blood and regulate their bioavailability.[1] Emerging evidence has shown that low levels of SHBG are associated with T2D.[2] Genetic factors are important factors that affect the development of T2D. However, the combined effect of SHBG and genetic factors on T2D risk is largely unknown. In the current study, we analyzed data from the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) to evaluate whether SHBG levels could interact with genetic predisposition to increase the T2D risk in men and postmenopausal women and examined the joint association of SHBG and genetic predisposition with T2D.

The data were from the SPECT-China study from February 2014 to May 2016. Subjects who were 18–80 years old ($n = 12,666$) were recruited. Men and postmenopausal women ($n = 9423$) were eligible for inclusion. Participants who had missing information on more than two single nucleotide polymorphism (SNP) genotypes ($n = 1618$), missing SHBG data ($n = 330$), or use of estrogen replacement therapy ($n = 0$) were excluded. Finally, this study included a total of 7475 men and postmenopausal women. The workflow of this research is shown in Supplementary Figure 1, http://links.lww.com/CM9/B699. The study received approval from the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (No. SH9H-2013-86). Written informed consent was obtained from all study participants. Demographic characteristics, lifestyle risk factors, bodyweight, height, blood pressure, interviews, and biological specimens at each site were collected with a uniform assessment protocol, and blood samples were obtained in a central laboratory as before.[3] Eighteen SNPs associated with T2D and identified from large-scale genome-wide association studies and meta-analyses in East Asians were selected[3] [Supplementary Table 1, http://links.lww.com/CM9/B699], and then we successfully constructed a weighted diabetes genetic risk score in Chinese adults using an additive model. Logistic regression models were used to examine the association of SHBG and genetic risk with T2D in men and postmenopausal women. The interaction analysis between SHBG quartiles and diabetes genetic-risk tertiles was performed. All analyses were two-sided. *P*-values <0.05 indicated significant differences.

In the current study, 4050 men and 3425 postmenopausal women were included. The baseline characteristics are presented in Supplementary Table 2, http://links.lww.com/CM9/B699. After multivariable adjustment in Model 3, there was a significant inverse relationship between SHBG quartiles and diabetes [Supplementary Table 3, http://links.lww.com/CM9/B699]. The relationship remained significant after further adjustment for diabetes genetic risk score. Each 1-standard deviation (SD) decrease in log-serum SHBG was associated with a 4% increased risk of diabetes in men and a 132% increased risk of diabetes in postmenopausal women in Model 4. We also found a positive association between weighted genetic risk-score tertiles and diabetes in both men and postmenopausal women [Supplementary Table 4, http://links.lww.com/CM9/B699]. Each 1-SD increase in the genetic risk score was associated with a 23% increased risk of diabetes both in men and in postmenopausal women in Model 4. When considered jointly, the highest odds of diabetes were observed in high genetic-risk participants with the lowest SHBG quartile [Figure 1]. Compared with low genetic-risk participants with the highest quartile of SHBG, the lowest SHBG quartile was associated with adjusted odd ratios (ORs) (95% confidence interval [CIs]) of 3.78 (2.23, 6.42) among those at low genetic risk, 4.33 (2.58, 7.26) among those at interme-

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Correspondence to: Yingli Lu, Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200011, China
E-Mail: luyingli2008@126.com

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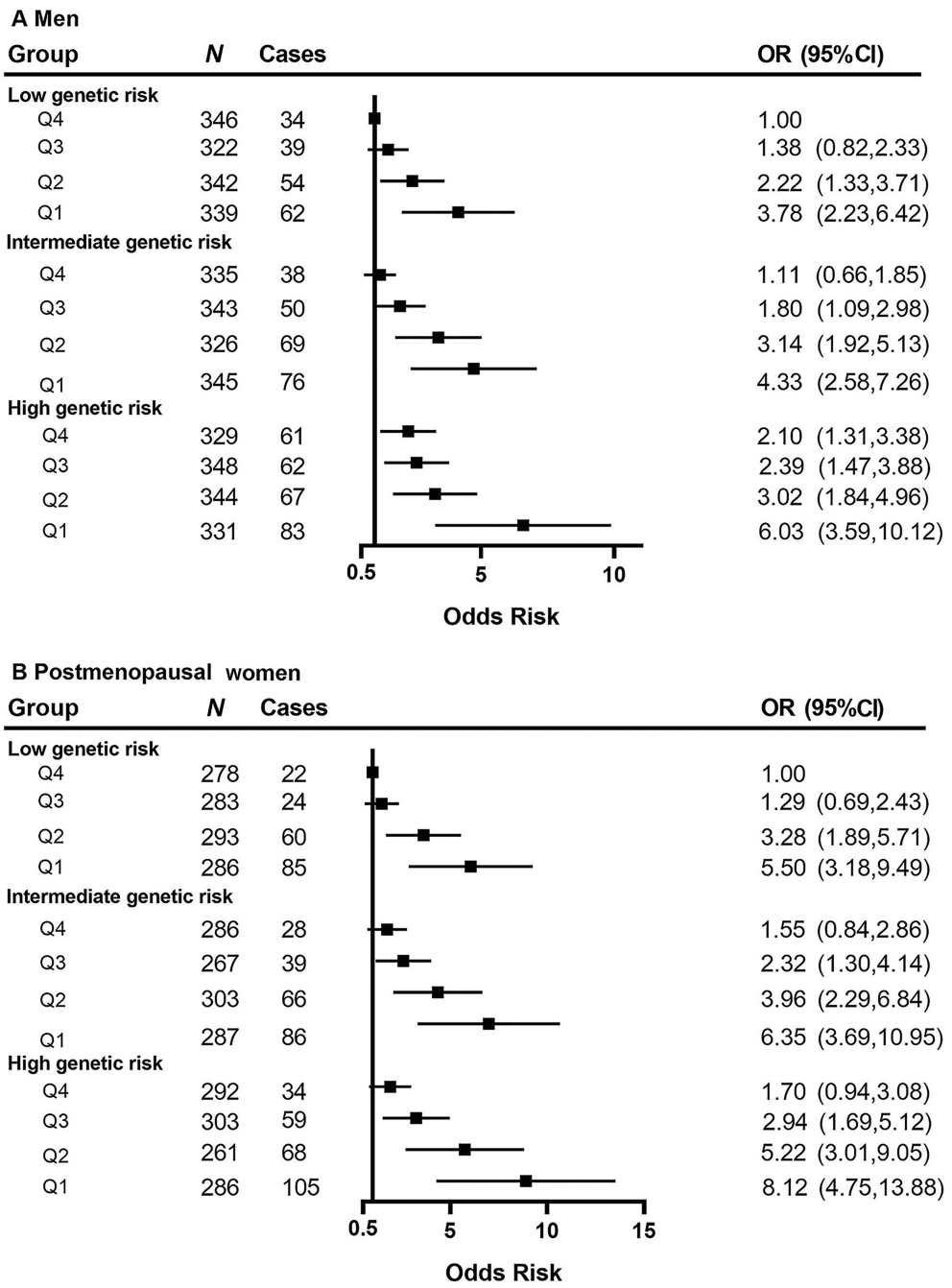

Figure 1: Multivariable-adjusted ORs (95% CI) for T2D according to the quartiles of SHBG and weighted genetic risk in men (A) and postmenopausal women (B). Participants at the highest quartile of SHBG with low genetic risk served as the reference group. The models were adjusted for age, education level, smoking status, drinking status, family history of diabetes, BMI, SBP, total cholesterol, and ln-total testosterone. BMI: Body mass index; CI: Confidence interval; ORs: Odds ratios; SBP: Systolic blood pressure; SHBG: Sex hormone-binding globulin; T2D: Type 2 diabetes.

diate genetic risk, and 6.03 (3.59, 10.12) among those at high genetic risk in men. The corresponding adjusted ORs (95% CIs) in postmenopausal women were 5.50 (3.18, 9.49), 6.35 (3.69, 10.95), and 8.12 (4.75, 13.88), respectively. There were no significant interactions between the SHBG quartiles and genetic risk (all $P_{interaction}$ >0.05). The sensitivity analyses using unweighted genetic risk-score tertiles showed similar results [Supplementary Table 5, http://links.lww.com/CM9/B699].

In the current study, we found that lower serum SHBG levels were significantly associated with an increased T2D risk in Chinese men and postmenopausal women regardless of genetic risk status. Genetic susceptibility and SHBG might exert an additive effect on T2D development. Our study extends the existing evidence showing an inverse association between SHBG levels and T2D risk.[4] Our findings reported that compared with those at low genetic risk with high SHBG levels, participants with both a high genetic risk and low

SHBG levels had the highest T2D risk. These results support the notion that low SHBG levels may increase predisposition to T2D in adulthood regardless of genetic risk, which implies the importance of maintaining a healthy lifestyle for the prevention of T2D in those with low SHBG levels. Alternatively, intensive measures may target populations with high genetic risk and low SHBG levels. Several potential mechanisms underlying the association between low SHBG levels and T2D later in life have been proposed. Previous studies indicated that circulating SHBG is predictive of the degree of insulin resistance and glycemia at the 6-year follow-up.[5] Mendelian randomization results suggested that SHBG is a hepatokine involved in the pathogenesis of T2D in women.[5] The exact role of SHBG in the development of T2D remained to be clarified.

However, our study also has several limitations. First, it has a cross-sectional design, and we could not draw conclusions regarding the causal relationship between serum SHBG and diabetes prevalence. Second, we constructed a genetic risk score based on only 18 common SNP genotypes, which may not fully reflect the genetic profile of diabetes. Moreover, since the present analyses were performed in Chinese individuals using SNPs identified in East Asians, our results might not be directly generalizable to other ethnic groups. Finally, information on several factors potentially affecting diabetes risk, such as maternal health and adult dietary patterns, was not collected. Therefore, the possibility of residual confounding cannot be ruled out.

In conclusion, independent of the genetic risk score, lower serum SHBG levels were significantly associated with an increased T2D risk in Chinese men and postmenopausal women. Further studies are needed to investigate the causal relationship and the underlying mechanisms.

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Conflicts of interest

None.

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