Obesity Facts
The European Journal of Obesity

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490
Received: February 9, 2019
Accepted: April 16, 2019
Published online: June 5, 2019

Research Article

Sexual Dimorphism of a Genetic Risk Score for Obesity and Related Traits among Chinese Patients with Type 2 Diabetes

Xiaomu Kong Xiaoyan Xing Xuelian Zhang Jing Hong Wenying Yang

Department of Endocrinology, China-Japan Friendship Hospital, Beijing, PR China

Keywords

Obesity · Type 2 diabetes · Genetic risk score · Sex dimorphism · Single-nucleotide polymorphism

Abstract

Background: Obesity is more prevalent in men than in women in China, especially within the middle-aged population. ***Objectives:*** The present study aims to determine the contribution of sexual dimorphisms to obesity and related traits in terms of the mechanisms involving the obesity-related genetic variants among patients of Chinese Han ancestry with type 2 diabetes. ***Method:*** In the Chinese National Diabetes and Metabolic Disorders Study, 2,555 out of 4,036 patients with type 2 diabetes were treatment naive, including 1,142 men and 1,413 women. Single-nucleotide polymorphisms (SNP) from 18 genomic loci previously found to be associated with obesity-related traits were successfully genotyped, and a genetic risk score (GRS) was constructed by summing the risk alleles for obesity. ***Results:*** Single SNP analysis showed that genetic variants in *SLC30A10, TMEM18, GNPDA2, PRL, TFAP2B, BDNF, MTCH2, FTO,* and *MC4R* were nominally associated with waist circumference (WC), BMI, and risk for abdominal or general obesity in the untreated patients with type 2 diabetes, as well as in the total group of patients with type 2 diabetes (untreated and treated) ($p < 0.05$). Interactions between sex and SNP in *PRL, MTCH2,* and *FTO* were detected ($p < 0.05$). In the untreated patients with diabetes, the GRS was nominally associated with WC (β = 0.0032, SE = 0.0011; $p = 0.003$), BMI (β = 0.0030, SE = 0.0013; $p = 0.027$), and increased risk for abdominal (OR = 1.08; 95% CI 1.02–1.13; $p = 0.004$) or general obesity (OR = 1.07; 95% CI 1.02–1.13; $p = 0.011$) in men but not in women. GRS-sex interactions were detected in the determinant of WC ($p = 0.019$) and abdominal obesity ($p = 0.016$). Among patients aged 30–60 years, GRS was found to be significantly associated with WC (β =

Wenying Yang, MD
Department of Endocrinology, China-Japan Friendship Hospital
No. 2 Yinghua East St., Chaoyang District
Beijing 100029 (PR China)
E-mail ywying_1010@163.com

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

0.0050, SE = 0.0016; p = 0.002) and abdominal obesity (OR = 1.10; 95% CI 1.04–1.17; p = 0.001) and nominally associated with BMI (β = 0.0057, SE = 0.0020; p = 0.005) and general obesity (OR = 1.07; 95% CI 1.01–1.14; p = 0.027) in men, whereas in women none of the associations were detected. GRS-sex interactions were present in the determinant of WC (p = 0.015), BMI (p = 0.032), and abdominal obesity (p = 0.012). Among patients aged 60 years or older, neither an association of GRS with obesity-related traits nor GRS-sex interactions were detected. ***Conclusions:*** Genetic factors contribute to obesity-related traits in a sex-dependent pattern among middle-aged Chinese, and men tend to be more susceptible to the genetic risk of obesity.

Introduction

Obesity is a major risk factor for type 2 diabetes, and the growing obesity epidemic is contributing to an increased prevalence of type 2 diabetes [1]. Obesity, diabetes, and related complications are posing an ever-increasing burden for healthcare systems worldwide. In China, specifically, there have been rapid increases in the obese population and patients with diabetes in recent decades. Moreover, in China, both obesity and diabetes are more prevalent in men than in women [2, 3]. As reported by the Chinese National Diabetes and Metabolic Disorder Study (DMS), the prevalence of diabetes and overweight/obesity (defined by a BMI ≥25) were 10.6 and 36.67%, respectively, in men versus 8.8 and 29.77%, respectively, in women. Interestingly, with stratification of the population into 10-year age groups, the prevalence of diabetes was greater in men than in women within the 30- to 60-year age groups only, and it was not observed in the populations 60 years old or older [2]. For obesity, a similar trend in sex-differentiated prevalence has been observed; that is, the proportion of men with a BMI ≥25 is greater than that of women, particularly within the 30- to 50-year age groups and not in the elderly groups. Thus, we speculated that the sex-based difference in the prevalence of diabetes could, at least partially, be explained by the sex-based difference in the prevalence of obesity. However, the underlying mechanisms remain unclear. A more complete understanding of the sex-specific risk factors for obesity in different age groups would be beneficial for personalized prevention of both obesity and diabetes in the Chinese population.

Both obesity and its-related traits are heritable. Studies have reported that the heritability of BMI ranges between 41 and 90% as estimated by the twin methodology, whereas the heritability of waist circumference (WC) is approximately 39%, suggesting a strong genetic predisposition for obesity [4, 5]. It has also been indicated that women exhibit a larger heritability of adipose distribution traits, such as WC and waist-hip ratio (WHR), than men, suggesting the involvement of substantial underlying sex-specific genetic components [6]. For instance, in both the Framingham Heart Study and the TwinGene study, variance component analyses demonstrated that the heritability of WHR adjusted for BMI (WHRadjBMI) in women (n = 46; 56%) was significantly larger than in men (n = 19; 32%) [7]. In 2,506 Dutch individuals from the Erasmus Rucphen Family study, significantly higher heritability rates for WC and WHR in women (n = 50; 49%) were reported than in men (n = 38; 42%) [8]. However, studies focused on sex differences in heritability of general obesity traits, such as BMI, have shown inconsistent results [5]. A meta-analysis reported similar overall heritability estimates for men (73%) and women (75%) and demonstrated that sex had no effect on the heritability estimate of BMI [4]. Massive genetic loci influencing obesity-related traits have been identified in sex-combined populations through genome-wide association studies (GWAS) and candidate gene approaches, including *NEGR1, SEC16B, SLC30A10, TMEM18, ETV5/DGKG,*

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

GNPDA2, BAT2, PRL, TFAP2B, MSRA, BDNF, MTCH2, FAIM2, FTO, MAF, MC4R, NPC1, KCTD15, etc. [9]. Several studies have further assessed the sex-dependent effects [10–13]. Moreover, novel sexual-dimorphic genetic loci have been identified via sex-stratified GWAS [7, 14, 15]. Sex-specific studies have also demonstrated strong sexual dimorphisms in the genetic regulation of adipose distribution traits, such as WC, but not in the determinant of general obesity [7, 14, 15].

Notably, most of the current findings on sexual dimorphic genes have been obtained in the Caucasian population, and such evidence for East Asian populations is lacking. However, strong ethnicity-based differences in body composition and fat distribution between Caucasians and East Asians have been demonstrated [1, 16]. Briefly, East Asians with a similar BMI have increased visceral obesity compared to Caucasians, suggesting a distinguishing pathogenesis of obesity between these ethnicities [1]; thus, there is a great need for ethnicity-specific studies.

In the present study, we recruited untreated Chinese patients with type 2 diabetes from the DMS and investigated potential associations of an obesity-related genetic risk score (GRS) with obesity-related traits in men and women, separately. The GRS-sex interactions on the determinant of obesity in these patients were also examined. Importantly, upon dividing the patients into 30- to 60-year or ≥60-year age groups, sex-specific genetic effects were further explored in the middle-age and elderly patients separately. The current study provides evidence for a sex-specific genetic basis of obesity in the Chinese population, and these results improve the current knowledge of the pathogenesis of obesity and diabetes and can be applied in the establishment of effective personalized methods for the prevention of these conditions in the future.

Materials and Methods

Study Participants

The study participants were recruited from the DMS [2]. A 75-g oral glucose tolerance test was given to all of the participants after overnight fasting. Type 2 diabetes was identified according to the 1999 World Health Organization (WHO) criteria or a self-reported history of type 2 diabetes. Initially, we included 2,555 patients with type 2 diabetes who had not been treated with any anti-diabetic therapy at enrolment, including 1,142 men and 1,413 women (Table 1). The analyses were also conducted in 4,036 patients with type 2 diabetes, including both untreated and treated patients (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000500490).

Definitions of Abdominal Obesity and General Obesity

An amended definition for the Chinese Han population was used to define abdominal obesity as a WC ≥90 cm for men and ≥85 cm for women [17]. General obesity in the Chinese population was defined as a BMI ≥28 [18].

Clinical Measurements and Laboratory Methods

Body weight and WC were measured using standard methods by trained staff at enrolment. BMI was calculated as weight/height^2 (kg/m^2). Each participant completed a standard 75-g oral glucose tolerance test after overnight fasting. Blood samples were drawn at 0 and 30 min and 2 h after the oral glucose tolerance test for measurement of plasma glucose and serum insulin concentrations as described previously [19].

Obesity Facts
The European Journal of Obesity
Obes Facts 2019;12:328–343
DOI: 10.1159/000500490
www.karger.com/ofa

Table 1. Clinical characteristics of the treatment-naive type 2 diabetes patients included in this study

Trait	Treatment-naive type 2 diabetes (n = 2,555)			Treatment-naive type 2 diabetes (30 ≤ age < 60 years) (n = 1,684)			Treatment-naive type 2 diabetes (age ≥60 years) (n = 784)		
	men	women	p	men	women	p	men	women	p
Sample size, n	1,142	1,413		756	928	–	331	453	–
Age, years	52.00 (44.00–61.00)	55.00 (46.00–63.00)	**2.39×10^{-6}**	48.00 (42.00–53.00)	50.00 (44.00–55.00)	**1.65×10^{-4}**	67.00 (63.00–71.00)	67.00 (63.00–71.00)	0.776
BMI	26.23 (23.92–28.73)	25.82 (23.52–28.37)	**0.035**	26.53 (24.35–28.90)	25.82 (23.53–28.40)	**0.003**	25.65 (23.00–28.08)	25.92 (23.51–28.16)	0.352
WC, cm	91.00 (85.00–98.00)	86.00 (80.00–92.00)	**6.18×10^{-38}**	92.00 (86.00–98.00)	85.00 (79.00–91.00)	**1.94×10^{-40}**	91.00 (84.00–97.00)	88.00 (81.00–94.00)	**1.41×10^{-4}**
General obesity	362 (31.73)	394 (27.98)	**0.040**	259 (34.26)	266 (28.66)	**0.014**	84 (25.38)	120 (26.49)	0.726
Abdominal obesity	659 (57.91)	775 (55.00)	0.142	447 (59.36)	488 (52.53)	**0.005**	188 (56.80)	277 (61.28)	0.207
Fasting plasma glucose, mmol/L	7.19 (6.11–8.42)	7.19 (6.11–8.41)	0.644	7.20 (6.14–8.49)	7.22 (6.17–8.48)	0.644	7.09 (6.0– 8.35)	7.04 (6.05–8.30)	0.704
2-h OGTT glucose, mmol/L	12.73 (11.20–15.80)	12.79 (11.21–16.18)	0.435	12.70 (11.24–15.83)	12.65 (11.12–16.02)	0.324	13.06 (11.29–16.15)	13.20 (11.42–16.44)	0.052
GRS	19.00 (17.00–21.00)	19.00 (17.00–21.00)	0.949	19.00 (17.00–21.00)	19.00 (18.00–21.00)	0.642	19.00 (18.00–21.00)	19.00 (17.00–21.00)	0.541
$N_{T1(9-18)}/N_{T2(19-20)}/N_{T3(21-27)}$	447/351/344	564/437/412	0.860	301/228/227	365/284/279	0.974	124/107/100	185/143/125	0.593

Data are shown as medians (IQR) or numbers (%) unless otherwise stated. p values were calculated to assess intergroup differences using a χ^2 test or a t test. Prior to the t test, all quantitative traits with a non-gaussian distribution were transformed (natural logarithm) to normalize distributions. OGTT, oral glucose tolerance test. p values <0.05 are denoted in bold. p values $<1.85\times10^{-3}$ which were statistically significant after Bonferroni correction (0.05/27) are denoted in bold and underlined.

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

Genotyping

Genomic DNA samples were extracted from peripheral blood using a DNA extraction kit (Biotek, Beijing, China). We selected 27 single-nucleotide polymorphisms (SNP) from 25 genetic loci that had been identified as being associated with BMI, body weight, WC, or obesity status by previous GWAS and validated in several populations, including rs2568958-*NEGR1*, rs10913469-*SEC16B*, rs2605100-*SLC30A10*, rs7561317-*TMEM18*, rs7647305-*ETV5/DGKG*, rs10938397-*GNPDA2*, rs6232-*PCSK1*, rs2260000-*BAT2*, rs4712652-*PRL*, rs987237-*TFAP2B*, rs545854-*MSRA*, rs10508503-*PTER*, rs6602024-*PFKP*, rs4923461-*BDNFOS*, rs925946-*BDNF*, rs10838738-*MTCH2*, rs7138803-*FAIM2*, rs8050136-*FTO*, rs9939609-*FTO*, rs10146997-*NRXN3*, rs1424233-*MAF*, rs7498665-*SH2B1*, rs12970134-*MC4R*, rs1805081-*NPC1*, rs11084753- *KCTD15*, rs29941-*KCTD15*, and rs6013029-*CTNNBL1* [9, 20–30]. Genotyping was performed using the Illumina GoldenGate Indexing Assay (Illumina Inc., San Diego, CA, USA) according to the manufacturer's instructions. SNP with genotyping call rates <85% (rs7498665 from *SH2B1* and rs11084753 and rs29941 near *KCTD15*) or a minor allele frequency <1% (rs10508503 near *PTER*, rs6232 in *PCSK1*, rs6602024 in *PFKP*, rs6013029 in *CTNNBL1*, and rs10146997 in *NRXN3*) in the type 2 diabetes population were excluded. Rs9939609 in *FTO* was excluded because it is in the same linkage region as rs8050136 (r^2 = 1). Thus, 4,036 participants with complete genotyping data for the remaining 18 SNP were included in the analysis. Based on the 229 genotyping duplicates, the concordance rate was 100%. Information related to the SNP is listed in online supplementary Table 2.

Statistical Analysis

The Hardy-Weinberg equilibrium test was performed for each SNP using a χ^2 test in the study population (online suppl. Table 2). An obesity-related GRS was constructed and calculated for each participant by summing the risk alleles of the 18 SNP (rs2568958-*NEGR1*, rs10913469-*SEC16B*, rs2605100-*SLC30A10*, rs7561317-*TMEM18*, rs7647305-*ETV5/DGKG*, s10938397-*GNPDA2*, rs2260000-*BAT2*, rs4712652-*PRL*, rs987237-*TFAP2B*, rs545854-*MSRA*, rs4923461-*BDNFOS*, rs925946-*BDNF*, rs10838738-*MTCH2*, rs7138803-*FAIM2*, rs8050136-*FTO*, rs1424233-*MAF*, rs12970134-*MC4R*, and rs1805081-*NPC1*) that had been reported as contributing to the increased risk of obesity (online suppl. Table 2). The distribution of GRS in the population is shown in online supplementary Figure 1.

To eliminate the potential influence of hypoglycemic treatments on obesity traits, we further conducted separate analyses including only treatment-naive patients with type 2 diabetes and then all patients, separately. The associations of genetic factors and phenotypes were examined in the following groups: untreated patients with type 2 diabetes (n = 2,555), untreated patients aged 30–60 years (n = 1,684), untreated patients aged ≥60 years (n = 784), patients with type 2 diabetes (n = 4,036), patients aged 30–60 years (n = 2,480), and patients aged ≥60 years (n = 1,451). Non-gaussian distributed quantitative traits were natural logarithmically transformed to normal distributions. Linear regression models were used to test the associations of GRS with BMI or WC, as well as the associations of single SNP and traits under the additive genetic assumption (Table 2; online suppl. Tables 3, 4). Logistic regression models were applied to test the associations of GRS and single SNP with the risk for obesity under the additive genetic assumption (Table 3; online suppl. Tables 5, 6). Age and sex were used as confounders to adjust the analyses in the models described above. To examine the gene-sex interaction, age, sex, GRS (or single SNP), and the interaction term (GRS [or single SNP] × sex) were further included in the logistic model or the general linear regression model. Moreover, the associations of GRS with obesity-related traits were examined in men and women, separately, with adjustment for age in the models.

Obesity Facts
The European Journal of Obesity
Obes Facts 2019;12:328–343
DOI: 10.1159/000500490
www.karger.com/ofa

Table 2. Associations of GRS with WC and BMI in treatment-naive type 2 diabetes

GRS group	Trait	Treatment-naive type 2 diabetes			Treatment-naive type 2 diabetes (30 ≤ age < 60 years)			Treatment-naive type 2 diabetes (age ≥60 years)		
		all (n = 2,555)	men (n = 1,142)	women (n = 1,413)	all (n = 1,684)	men (n = 756)	women (n = 928)	all (n = 784)	men (n = 331)	women (n = 453)
T1 (9–18)	WC, cm	88.00 (82.00–94.00)	90.00 (84.00–96.00)	86.15 (80.00–92.00)	88.00 (82.00–94.00)	90.00 (84.00–97.00)	86.00 (80.00–90.00)[b]	89.00 (82.00–94.00)	90.00 (84.00–95.00)	88.00 (80.00–93.00)
T2 (19–20)	WC, cm	88.00 (81.00–95.00)	91.00 (85.00–97.00)	86.00 (80.00–92.00)	88.00 (80.00–95.00)	92.00 (86.50–99.00)[a]	84.00 (78.00–91.00)[b]	89.50 (83.00–96.00)	91.00 (86.00–97.00)	88.00 (82.00–94.00)
T3 (21–27)	WC, cm	89.00 (82.00–95.00)	92.00 (86.00–98.00)	86.00 (80.00v93.00)	89.00 (82.00–96.00)	93.00 (87.00–100.00)[a]	85.00 (80.00–92.00)[b]	89.00 (82.00–95.00)	91.00 (83.00–98.00)	87.00 (81.00–94.00)
GRS (increased by per allele)	β (SE)	0.0013 (0.0007)	0.0032 (0.0011)	0.0000 (0.0009)	0.0026 (0.0011)	0.0050 (0.0016)	0.0009 (0.0015)	0.0015 (0.0016)	0.0039 (0.0026)	−0.0002 (0.0021)
	p	0.065	**0.003**	0.964	**0.016**	**0.002**	0.518	0.376	0.140	0.913
	$p_{GRS \times sex}$	**0.019**	–	–	**0.015**	–	–	0.571	–	–
T1 (9–18)	BMI	25.72 (23.50–28.16)	25.64 (23.64–28.09)	25.80 (23.37–28.20)	25.97 (23.83–28.44)	26.08 (23.94–28.69)	25.95 (23.81–28.28)	25.64 (23.15–28.12)	25.19 (22.85–27.40)	25.97 (23.31–28.44)
T2 (19–20)	BMI	25.58 (23.34–28.04)	25.82 (23.67–28.20)	25.27 (22.96–27.86)	25.83 (23.57–28.48)	26.60 (24.52–28.99)	25.25 (22.94–27.98)[b]	25.70 (23.53–28.08)	25.69 (22.86–28.26)	25.71 (23.77–27.97)
T3 (21–27)	BMI	25.96 (23.61–28.63)	26.23 (24.03–28.72)	25.77 (23.41–28.48)	26.37 (24.16–29.24)[a]	26.67 (24.68–29.30)[a]	26.11 (23.73–29.17)	26.22 (23.32–28.31)	26.15 (23.13–28.57)	26.22 (23.48–28.12)
GRS (increase per allele)	β (SE)	0.0015 (0.0009)	0.0030 (0.0013)	0.0004 (0.0012)	0.0037 (0.0014)	0.0057 (0.0020)	0.0022 (0.0019)	0.0024 (0.0021)	0.0047 (0.0033)	0.0008 (0.0028)
	p	0.104	**0.027**	0.742	**0.008**	**0.005**	0.236	0.265	0.151	0.780
	$p_{GRS \times sex}$	0.149	–	–	**0.032**	–	–	0.812	–	–

Data are shown as medians (IQR) unless otherwise stated. In men or women populations, β coefficients and SE were determined for the GRS using multivariate linear regression adjusted for age. In sex-combined populations, β coefficients and SE were determined for the GRS using multivariate linear regression adjusted for age and sex. The interaction term (GRS × sex) was further included in the generalized linear models to assess the interaction between GRS and sex. Prior to the comparisons of clinical characteristics, all quantitative traits with a non-gaussian distribution were transformed (natural logarithm) to normalize distributions. [a] Different compared to T1 within the same population. [b] Different compared to men within the same GRS subgroup. p values < 0.05 are denoted in bold. p values <2.78 × 10^{-3} which were statistically significant after Bonferroni correction (0.05/18) are denoted in bold and underlined.

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

The participants were divided into 3 approximately equally sized tertiles according to GRS (lowest GRS group, T1: 9–18; middle GRS group, T2: 19–20; and highest GRS group, T3: 21–27) in treatment-naive diabetes ($N_{T1}/N_{T2}/N_{T3}$ = 447/351/344), as well as in overall type 2 diabetes ($N_{T1}/N_{T2}/N_{T3}$ = 684/547/534) [31, 32]. Logistic regression models were further used to examine the contribution of the highest-GRS (T3) and middle-GRS (T2) groups compared to the lowest-GRS group (T1) to the risk for abdominal obesity or general obesity (Table 3; online suppl. Table 6).

Bonferroni correction was used to correct multiple testing in the above comparisons. Results were considered significant according to threshold *p* values calculated as 0.05 divided by the times of comparison which are shown in the table footnotes. In addition, a nominal association was considered for *p* values between the significant thresholds and 0.05 [33].

Analysis of variance (ANOVA) and Student-Newman-Keuls analysis were applied for comparisons of intergroup differences within the lowest-GRS (T1), middle-GRS (T2), and highest-GRS (T3) groups (Table 2; online suppl. Table 4).

Statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC, USA) and PLINK software (v1.07).

Power Calculation

The sample sizes in this study had >80% power to detect the association of GRS and obesity-related indices with an effect size of 0.02 at $\alpha = 0.05$. Power calculations were performed using G*power 3.0 software (http://www.gpower.hhu.de/).

Results

Clinical Characteristics of the Study Population

All SNP adhered to Hardy-Weinberg equilibrium. The minor allele frequencies of the genotyped SNP in the present study were close to those reported for a Han Chinese population from Beijing in HapMap (online suppl. Table 2). The GRS constructed by risk allele for obesity were comparable between men and women in patients with type 2 diabetes and each subgroup (*p* value range: 0.541–0.997) (Table 1; online suppl. Table 1).

A total of 2,555 treatment-naive patients with type 2 diabetes, including 1,142 men and 1,413 women, were included in the current analyses. Among them, 1,684 patients were within the 30- 60-year age range, and 784 were 60 years or older. The clinical characteristics of the study populations are shown in Table 1 and were compared between men and women in the overall population and according to different age subgroups. Among treatment-naive patients with type 2 diabetes, men had a younger age than women, as well as a higher BMI and a larger WC, as expected (all $p < 0.05$). Within the 30- 60-year age groups similar differences were observed between men and women (WC: $p = 1.94 \times 10^{-40}$; BMI: $p = 0.003$), whereas within the ≥60-year group only WC showed a significant difference ($p = 1.41 \times 10^{-4}$). When using the Chinese criteria for abdominal and general obesity, significantly more patients with abdominal obesity (men vs. women 59.36 vs. 52.53%, $p = 0.005$) or general obesity (34.26 vs. 28.66%, $p = 0.014$) were observed in the male groups than in the female groups within the age range of 30–60 years, but this difference was not observed for patients aged ≥60 years ($p = 0.207$ and 0.726). Similar findings for WC and BMI were found in the larger population including both untreated and treated patients with type 2 diabetes, whereas a different proportion of abdominal obesity between men and women was only observed in the 30- to 60-year age groups (online suppl. Table 1).

Obesity Facts
The European Journal of Obesity
Obes Facts 2019;12:328–343
DOI: 10.1159/000500490
www.karger.com/ofa

Table 3. Associations of GRS with abdominal and general obesity in treatment-naive type 2 diabetes

Traits			Treatment-naive type 2 diabetes			Treatment-naive type 2 diabetes (30 ≤ age < 60 years)			Treatment-naive type 2 diabetes (age ≥60 years)		
			all (*n* = 2,555)	men (*n* = 1,142)	women (*n* = 1,413)	all (*n* = 1,684)	men (*n* = 756)	women (*n* = 928)	all (*n* = 784)	men (*n* = 331)	women (*n* = 453)
Abdominal obesity	*GRS group*										
	T1 (9–18)	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
	T2 (19–20)	OR (95% CI)	1.02 (0.85–1.24)	1.34 (1.01–1.77)	0.83 (0.65–1.07)	1.00 (0.79–1.26)	1.44 (1.01–2.04)	0.75 (0.54–1.02)	1.13 (0.80–1.59)	1.23 (0.73–2.07)	1.07 (0.68–1.67)
		p	0.803	**0.045**	0.158	0.995	**0.041**	0.069	0.485	0.447	0.784
	T3 (21–27)	OR (95% CI)	1.18 (0.97–1.43)	1.51 (1.13–2.01)	0.98 (0.76–1.27)	1.26 (0.99–1.59)	1.79 (1.25–2.55)	0.97 (0.70–1.33)	1.01 (0.71–1.44)	1.05 (0.62–1.78)	0.99 (0.62–1.57)
		p	0.089	**0.005**	0.891	0.055	**0.001**	0.826	0.947	0.866	0.955
	GRS (increase per allele)	OR (95% CI)	1.03 (1.00–1.06)	1.08 (1.02–1.13)	1.00 (0.95–1.04)	1.04 (1.00–1.08)	1.10 (1.04–1.17)	1.00 (0.95–1.05)	0.99 (0.93–1.06)	1.01 (0.92–1.11)	0.98 (0.91–1.06)
		p	0.095	**0.004**	0.804	**0.040**	**0.001**	0.100	0.823	0.824	0.625
		$p_{GRS \times sex}$	**0.016**	–	–	**0.012**	–	–	0.642	–	–
General obesity	*GRS group*										
	T1 (9–18)	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
	T2 (19–20)	OR (95% CI)	0.94 (0.77–1.61)	1.06 (0.78–1.44)	0.86 (0.65–1.14)	0.97 (0.75–1.25)	1.07 (0.74–1.55)	0.88 (0.62–1.26)	0.95 (0.65–1.40)	1.22 (0.66–2.22)	0.81 (0.49–1.33)
		p	0.579	0.729	0.299	0.797	0.722	0.498	0.801	0.526	0.408
	T3 (21–27)	OR (95% CI)	1.29 (1.05–1.58)	1.41 (1.04–1.91)	1.20 (0.91–1.59)	1.39 (1.08–1.77)	1.44 (1.01–2.07)	1.35 (0.96–1.90)	1.02 (0.69–1.50)	1.33 (0.72–2.44)	0.85 (0.51–1.41)
		p	**0.015**	**0.025**	0.191	**0.010**	**0.046**	0.082	0.930	0.358	0.523
	GRS (increase per allele)	OR (95% CI)	1.04 (1.00–1.07)	1.07 (1.02–1.13)	1.01 (0.96–1.06)	1.05 (1.01–1.09)	1.07 (1.01–1.14)	1.03 (0.97–1.09)	0.99 (0.93–1.06)	1.07 (0.96–1.19)	0.95 (0.87–1.03)
		p	0.054	**0.011**	0.741	**0.026**	**0.027**	0.292	0.841	0.252	0.230
		$p_{GRS \times sex}$	0.086	–	–	0.325	–	–	0.101	–	–

In male or female populations, OR and 95% CI were determined for the GRS or the T2 and T3 groups compared to the T1 group using logistic regression adjusted for age. In sex-combined populations, OR and 95% CI were determined for the GRS or the T2 and T3 groups compared to the T1 group using logistic regression adjusted for age and sex. The interaction term (GRS × sex) was further included in the logistic models to assess the interaction between GRS and sex. ref., reference. *p* values <0.05 are denoted in bold. *p* values $<1.39 \times 10^{-3}$ which were statistically significant after Bonferroni correction (0.05/36) are denoted in bold and underlined.

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

Associations of GRS with Obesity-Related Traits and GRS-Sex Interactions in the Overall Population

As shown in Tables 2 and 3, in the untreated patients, no associations were identified between GRS and any of the obesity-related traits including WC, BMI, abdominal obesity, and general obesity (p values range: 0.054–0.104). When the population was stratified by sex, GRS showed a nominal association with WC (β = 0.0032, SE = 0.0011; p = 0.003) and a nominal association with BMI (β = 0.0030, SE = 0.0013; p = 0.027) in men but not in women. GRS increased the risk for abdominal obesity or general obesity by 1.08- or 1.07-fold per allele specifically in men (p = 0.004 and 0.011), and the group with the highest genetic risk for obesity (T3) showed a 1.51- or 1.41-fold risk for abdominal obesity or general obesity (p = 0.005 and 0.025) compared to the group with the lowest genetic risk (T1). Moreover, GRS-sex interactions were identified in the GRS association with WC or abdominal obesity ($p_{GRS \times sex}$ = 0.019 and 0.016).

In the overall type 2 diabetes population, associations of GRS with WC (β = 0.0023, SE = 0.0009; p = 0.013) and BMI (β = 0.0035; SE = 0.0012; p = 0.002) were identified in the sex-combined group. Moreover, significant associations of GRS with WC (β = 0.0046, SE = 0.0014; $p = 8.76 \times 10^{-4}$) and BMI (β = 0.0057, SE = 0.0017; $p = 9.29 \times 10^{-4}$), as well as nominal associations of GRS with abdominal (OR = 1.06; 95% CI1.02–1.10; p = 0.006) and general obesity (OR = 1.05; 95% CI 1.01–1.10; p = 0.029), were found in men but not in women (online suppl. Tables 4, 6). GRS-sex interactions were identified in the GRS association with WC and abdominal obesity ($p_{GRS \times sex}$ = 0.024 and 0.004) (online suppl. Tables 4, 6).

In single marker analyses, SNP in *SLC30A10, TMEM18, GNPDA2, TFAP2B, BDNF, MTCH2, FTO,* and *MC4R* were nominally associated with WC, BMI, and risk for abdominal or general obesity in treatment-naive patients and/or all patients with type 2 diabetes including both treated and untreated patients (online suppl. Tables 3, 5) (p value range: 0.039–2.79×10^{-4}). Interactions between SNP in *PRL, MTCH2,* and *FTO* and sex were identified (p value range: 0.013–0.049).

Associations of GRS with Obesity-Related Traits and GRS-Sex Interactions in Patients Aged 30–60 Years

In the untreated patients with type 2 diabetes aged 30–60 years, GRS was nominally associated with WC (β = 0.0026, SE = 0.0011; p = 0.016) and BMI (β = 0.0037, SE = 0.0014; p = 0.008) and it was associated with increased risks for both abdominal obesity (OR = 1.04; 95% CI 1.00–1.08; p = 0.040) and general obesity (OR = 1.05; 95% CI 1.01–1.09; p = 0.026) in the sex-combined population. The T3 group showed a significantly higher BMI (median: 25.97, IQR 24.16–29.24) than T1 group (median: 25.97, IQR 23.83–28.44).

With patient stratification by sex, a significant association of GRS with WC (β = 0.0050, SE = 0.0016; p = 0.002), as well as a nominal association with BMI (β = 0.0057, SE = 0.0020; p = 0.005), was identified in men. Compared to the T1 group, men with the middle genetic risk (T2) and the largest genetic risk (T3) showed a significantly larger WC (T1: median: 90.00, IQR 84.00–97.00; T2: median: 92.00, IQR 86.50–99.00; and T3: median: 93.00, IQR 87.00–100.00), and the T3 group had a higher BMI (T1: median: 26.08, IQR 23.94–28.69; T3: median: 26.67, IQR 24.68–29.30). Meanwhile, GRS significantly increased the risk for abdominal obesity by 1.10-fold (p = 0.001) and nominally increased the risk for general obesity by 1.07-fold (p = 0.027) per allele in men. The T3 group showed a 1.79- or 1.44-fold risk for abdominal obesity or general obesity (p = 0.001 and 0.046) compared to the T1 group. However, no associations were detected in women. Interaction effects of GRS and sex on the determinant of WC and BMI were observed ($p_{GRS \times sex}$ = 0.015 and 0.032) as well as on the risk for abdominal obesity ($p_{GRS \times sex}$ = 0.012; Tables 2, 3).

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

In all patients with type 2 diabetes (both treated and untreated) within the 30- to 60-year age range, GRS was associated with WC (β = 0.0019, SE = 0.0009; p = 0.033). However, GRS was not associated with BMI or abdominal obesity or general obesity in these analyses, suggesting the possibility of confounding effects of antidiabetic therapies. In men, GRS was associated with WC (β = 0.0037, SE = 0.0013; p = 0.005), BMI (β = 0.0033, SE =0.0016; p = 0.043) and the risk for abdominal obesity (OR = 1.08; 95% CI 1.03–1.13; p = 0.002), which were not observed in women (online suppl. Tables 4, 6). GRS-sex interactions were identified on the determinant of WC, BMI, and the risk for abdominal obesity ($p_{GRS \times sex}$ = 0.017, 0.046, and 0.008; online suppl. Tables 4, 6).

Associations of GRS with Obesity-Related Traits and GRS-Sex Interactions in Patients Aged 60 Years or Older

In the treatment-naive patients aged 60 years or older, no associations were detected between GRS and any of the obesity-related traits in the sex-combined male or female populations (p value range: 0.151–0.913). Moreover, GRS-sex interactions were not identified (p value range: 0.101–0.812) (Tables 2, 3).

In all patients with type 2 diabetes (both treated and untreated) aged 60 years or older, no associations were observed except for a nominal association of GRS with the risk for general obesity in men (OR = 1.09; 95% CI 1.00–1.19; p = 0.048) (online suppl. Tables 4, 6).

Discussion/Conclusion

Epidemiological studies have indicated that both obesity and diabetes are more prevalent in middle-aged men than in middle-aged women of Chinese ancestry [2], but the underlying mechanisms require further investigation. The present study identified that a GRS based on risk alleles for obesity was associated with increased BMI and WC in the middle-aged (30–60 years) Chinese patients with type 2 diabetes as well as with the risk for abdominal obesity and general obesity. The sex-stratified analyses further revealed that these associations were significant in men but not in women. However, in the sex-combined population, GRS-sex interactions were detected in the determinant of BMI and WC, as well as the risk for abdominal obesity. However, none of the above findings were replicated in the elderly population (age ≥60 years). These findings suggest that men of Chinese ancestry are more susceptible to the genetic risk of obesity during the middle-aged period, which can partially explain the higher prevalence of obesity in middle-aged Chinese men versus women. As obesity is a major risk factor for diabetes, it could further contribute to the sex-differentiated prevalence rates of diabetes. To our best knowledge, this is the first study to demonstrate a role of genetic factors in the sex-dependent pathogenesis of obesity in middle-aged patients of Chinese ancestry with type 2 diabetes.

In the present study, we included both BMI and WC to assess general and abdominal obesity, respectively, as well as abdominal obesity and general obesity defined by Chinese criteria. WC as a measurement of abdominal obesity is more precise than BMI for assessing the obesity-related health burden, especially in East Asians [34–37]. In diabetes patients from Singapore, a higher WC corresponded to a greater risk of mortality at the same BMI level [38]. The ADVANCE study reported that abdominal measures are better predictors of cardiovascular diseases and mortality than BMI in type 2 diabetes [39]. Thus, the identification of risk factors for obesity and its related traits, especially risk factors for abdominal obesity, is important for the prevention of obesity and its related complications in type 2 diabetes.

Through GWAS approaches, many susceptibility SNP linked to obesity and its related traits have been identified [9, 20–30]. Our results confirmed that several SNP were nominally

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

associated with BMI, WC, or risk for obesity in patients with type 2 diabetes. However, none of the associations remained significant after Bonferroni corrections. In fact, complex traits, such as obesity, are known to be associated with massive genetic variants with small effective sizes, which partly explain why we were unable to detect any significant associations in single marker analyses. Thus, we constructed a GRS representing the cumulative effect of SNP in the analyses by adding the risk alleles, which was previously proven to be an effective tool to elucidate the overall genetic impact on obesity risk [31, 32]. The construction of GRS enables the identification of individuals with a high genetic risk who would probably benefit from genetically guided intensive interventions in the future.

Sexual dimorphisms in genetic susceptibility to obesity could be a key element contributing to the sex difference in the prevalence of obesity in Chinese. Based on previous epidemiological findings within different age range groups, sexual dimorphisms of obesity could be further inferred to be dependent on age [2, 3]. Therefore, patients were divided into middle-aged (30~60 years) and elderly groups (≥60 years) for separate analyses. The GRS levels were comparable between men and women in each age group, suggesting their common genetic background. For the middle-aged Chinese patients with diabetes, we found significant associations of WC and risk for abdominal obesity with GRS, as well as nominal associations of BMI and risk for general obesity with GRS, both of which were restricted to men. This suggested that middle-aged men are more susceptible to the genetic risk, which could then lead to the higher prevalence of obesity in middle-aged men than in middle-aged women, as shown in the DMS [2, 3]. As obesity is a causal factor for diabetes, this could further contribute to the higher prevalence of diabetes in middle-aged men than in middle-aged women of Chinese ancestry. Overall, the findings confirmed that genetic factors mainly contribute to the pathogenesis of obesity in middle-aged men of Chinese ancestry, whereas factors other than obesity susceptibility genes, such as hormonal changes, are major contributors to obesity in middle-aged women.

The mechanisms underlying the elevated susceptibility to genetic risk factors in middle-aged Chinese men remain to be elucidated. We speculated that it could partly be attributed to the interactions between genetic factors and aggregated harmful lifestyle factors. Gene-environment interaction plays an essential role in the determinant of complex trait/disease. For example, several studies have indicated that the estimated effective size of the risk alleles for obesity is more pronounced in smokers and individuals with a low physical activity [40–42]. In the Chinese population, lifestyle factors (such as smoking and less physical activity, etc.) are more frequently aggregated in men compared to women. In the DMS, 59.4% of men and 4.6% of women with newly diagnosed diabetes had smoked at least 100 cigarettes during their lifetime, whereas men were less physically active than women (assessed by regular leisure-time physical activity: men, 30.3%; women, 35.5%) [2]. Moreover, the smoking rate of the age groups 20–43 years (26.1%) and 44–52 years (27.1%) with newly diagnosed diabetes was higher than those for the age groups 53–61 years (17.5%) and >61 years (18.1%) [43]. Further investigations are warranted to confirm the interactions between GRS and lifestyle factors. Based on the results of this study, in middle-aged Chinese men, lifestyle interventions, such as smoking cessation and increased physical activity, can be beneficial by both reducing the conventional risk factors of obesity and modifying the genetic susceptibility.

Notably, the findings in the present study were opposite to those of previous reports that showed a greater genetic effect in women than in men. This could be explained by strong ethnicity differences in obesity. In the present study, all of the participants were of Chinese ancestry, whereas the majority of previous studies were conducted in Caucasians. As is well known, obesity is more prevalent in Caucasians than in Asians. Interestingly, in contrast to the epidemic status in China, epidemiological evidence has shown that in the USA, among mostly Caucasians, the prevalence of obesity (defined as a BMI ≥30) in women is significantly

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

higher than that in men across all age groups of adults. Among them, the 40- to 59-year age group showed the largest women-men disparity in obesity prevalence (women, 44.7%; men, 39.0%) [44]. In addition to the obesity rates, research has provided strong evidence for ethnicity differences in body composition and adipose distribution [1, 45]. East Asians have more body fat and a stronger tendency toward visceral adipose accumulation than Caucasians at any given BMI, suggesting ethnicity differences in the pathogenesis of obesity between Caucasians and East Asians. Thus, studies in specific ethnic populations are required in order to understanding the mechanisms underpinning obesity. As expected, the findings in our study, which differed from those obtained for Caucasian populations, supported the epidemiological trends of obesity in middle-aged Chinese individuals, which also differ from those in Caucasians.

Moreover, consistent with previous findings, GRS-sex interactions were mainly observed in the determinant of risk for abdominal obesity, but not for general obesity, suggesting that abdominal adipose distribution was more strongly affected by the sex-specific genetic susceptibility. Using the sex-specific GWAS approaches, previous studies based on populations with a large sample size have reported that genetic loci associated with body fat distribution traits (WC, WHR, and WHRadjBMI), but not overall obesity (BMI), show significant sexual dimorphisms [7, 14, 15]. A possible explanation could be the different underlying biological mechanisms of body mass traits and body fat distribution traits. For example, the results of GWAS showed a major neuronal component underpinning BMI but identified a group of genes that influence the early development and/or differentiation of adipocytes underlying WC and WHR [6]. Meanwhile, adipose tissue distributed in the abdominal viscera carry a much greater risk for adverse metabolic consequences than subcutaneous adipose tissue. The sex difference in visceral adipose tissue accumulation, which is partly explained by the findings in the current study from a genetic prospective, is an important criterion explaining sex differences in the cardiovascular risk profile [1, 34]. Therefore, it is suggested that gene-sex interactions in abdominal obesity should be emphasized in the prevention of obesity and its complications.

The rates of abdominal and general obesity in elderly men and women were comparable. Associations of GRS with obesity-related traits in the present study were not identified in either elderly men or elderly women, suggesting that genetic factors had a very little contribution in the elderly population. Numerous studies have indicated that hormonal factors contribute to obesity in the elderly, with the decline in testosterone being associated with an increased risk for obesity in aging men [46]. In women, aging is associated with a decline in estrogen, which is known to protect against weight gain by increasing energy expenditure. The loss of estrogen after menopause in women largely determines the shift of body shape toward a more androgynous type and results in abdominal fat accumulation [47]. Thus, modifiable behavioral factors (diet habit, physical activity, etc.) and healthy lifestyle instructions should be emphasized in the elderly Chinese to prevent obesity. Overall, the results suggest that obesity in the middle-aged and elderly population is attributable to different pathogenic mechanisms, and sex-stratified genetic studies based on ethnicity and age are warranted to achieve a more precise personalized intervention strategy in contrast to generalized comprehensive interventions.

The present study has the following strengths. First, the diabetes population was from a large and representative population with a high ethnic homogeneity in mainland China, which enables the results to be well generalizable in China. Second, this study was mainly based on untreated patients with diabetes to exclude the potential confounding effects of antidiabetic therapy on obesity. Third, the sex-dependent associations of GRS with obesity and its related traits were investigated separately within middle-aged and elderly patients for the first time. The results partly explain why obesity and diabetes are more prevalent in middle-aged

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

Chinese men versus women and suggest a sex-dependent pathogenesis of obesity. The present study further raises speculations that the sex-specific genetic effects on obesity could be dependent on ethnicity, which suggests that the existing evidence obtained in general Caucasian populations may not be generalizable to populations of other ethnicities. More data for specific populations and races need to be generated in the future.

This study also has some limitations. First, the results do not consider some of the uncovered obesity-related loci with sexual dimorphisms; only previously identified and well-replicated obesity-related loci were included, which were detected in sex-combined populations. Thus, sex-stratification is highly encouraged in such future studies. Second, interactions between genes and modifiable factors, such as diet, smoking, and physical activity, need to be investigated and analyzed in combination with the current findings to achieve a more precise and effective management of obesity.

In conclusion, within the middle-aged Chinese population with untreated type 2 diabetes, men were more susceptible to the genetic risk of obesity (especially the risk of abdominal obesity) than women, suggesting that the genetic architecture of adipose distribution functions differently in men and women. No associations between GRS and obesity-related traits were observed in the elderly populations. These findings indicate a role of sex-dependent mechanisms in the pathogenesis of obesity and further emphasize that personalized interventions based on ethnicity, sex, age, and genetic risk should be considered in the prevention and management of obesity.

Acknowledgement

We thank all of the patients for their participation in this study. We thank all of the staff of the DMS who contributed to recruiting participants and obtaining samples. We acknowledge the genotyping work of the Beijing Genomics Institute, Shenzhen, China.

Statement of Ethics

The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital in Beijing, and this study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the participants before data collection.

Disclosure Statement

This study was partly funded by the Sanofi (China) Investment Company Limited. There are no patents, products in development, or marketed products to declare. The funders had no role in the study design, data collection and analysis, the decision to publish, or the preparation of this paper. Outside of the submitted work, W.Y. has sat on the advisory board of Novo Nordisk, received investigator-initiated trial research funds from AstraZeneca, and been a speaker for Novo Nordisk, Bayer, Sanofi Aventis, Merck Sharp and Dohme China, AstraZeneca, Eli Lilly, Boehringer-Ingelheim, and Servier, and received honorarium and travel support as an advisory board member from Merck and Co., Inc. These do not alter our adherence to all of the journal policies on sharing data and materials, as detailed online in the guidelines for authors.

Funding Sources

This work was supported by grants from the Chinese Medical Association Foundation (http://en.cma.org.cn). This study was also partly funded by the Sanofi (China) Investment Company Limited (http://www.sanofi.cn/l/cn/zh/index.jsp).

Author Contributions

W.Y. generated the study hypothesis. W.Y. and X.K. developed the study design. X.X., X.Z., J.H., and X.K. collected the data. X.K. and W.Y. analyzed and interpreted the data. X.K. drafted this paper. W.Y., X.K., X.X., X.Z., and J.H. critically revised this paper and contributed to the Discussion. W.Y. completed the final version of this paper. All of the authors approved the submission of this work. W.Y. is the guarantor of this work.

References

1 Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013 Apr;1281(1):64–91.
2 Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med. 2010 Mar;362(12):1090–101.
3 Yang ZJ, Liu J, Ge JP, Chen L, Zhao ZG, Yang WY; China National Diabetes and Metabolic Disorders Study Group. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007-2008 China National Diabetes and Metabolic Disorders Study. Eur Heart J. 2012 Jan;33(2):213–20.
4 Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. Front Endocrinol (Lausanne). 2012 Feb;3:29.
5 van Dongen J, Willemsen G, Chen WM, de Geus EJ, Boomsma DI. Heritability of metabolic syndrome traits in a large population-based sample. J Lipid Res. 2013 Oct;54(10):2914–23.
6 Pulit SL, Karaderi T, Lindgren CM. Sexual dimorphisms in genetic loci linked to body fat distribution. Biosci Rep. 2017 Feb;37(1):R20160184.
7 Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, et al.; ADIPOGen Consortium; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GEFOS Consortium; GENIE Consortium; GLGC; ICBP; International Endogene Consortium; LifeLines Cohort Study; MAGIC Investigators; MuTHER Consortium; PAGE Consortium; ReproGen Consortium. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 2015 Feb;518(7538):187–96.
8 Zillikens MC, Yazdanpanah M, Pardo LM, Rivadeneira F, Aulchenko YS, Oostra BA, et al. Sex-specific genetic effects influence variation in body composition. Diabetologia. 2008 Dec;51(12):2233–41.
9 Herrera BM, Lindgren CM. The genetics of obesity. Curr Diab Rep. 2010 Dec;10(6):498–505.
10 Guclu-Geyik F, Onat A, Yuzbasıogulları AB, Coban N, Can G, Lehtimäki T, et al. Risk of obesity and metabolic syndrome associated with FTO gene variants discloses clinically relevant gender difference among Turks. Mol Biol Rep. 2016 Jun;43(6):485–94.
11 Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, et al.; MAGIC. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010 Nov;42(11):949–60.
12 Hubacek JA, Pitha J, Adamkova V, Lanska V, Poledne R. A common variant in the FTO gene is associated with body mass index in males and postmenopausal females but not in premenopausal females. Czech post-MONICA and 3PMFs studies. Clin Chem Lab Med. 2009;47(4):387–90.
13 Saldaña-Alvarez Y, Salas-Martínez MG, García-Ortiz H, Luckie-Duque A, García-Cárdenas G, Vicenteño-Ayala H, et al. Gender-Dependent Association of FTO Polymorphisms with Body Mass Index in Mexicans. PLoS One. 2016 Jan;11(1):e0145984.
14 Randall JC, Winkler TW, Kutalik Z, Berndt SI, Jackson AU, Monda KL, et al.; MAGIC Investigators. Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. PLoS Genet. 2013 Jun;9(6):e1003500.
15 Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, Chu S, et al.; CHARGE Consortium; DIAGRAM Consortium; GLGC Consortium; Global-BPGen Consortium; ICBP Consortium; MAGIC Consortium. The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. PLoS Genet. 2015 Oct;11(10):e1005378.

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

16 Haldar S, Chia SC, Henry CJ. Body composition in Asians and Caucasians: comparative analyses and influences on cardiometabolic outcomes. Adv Food Nutr Res. 2015;75:97–154.
17 Bao Y, Lu J, Wang C, Yang M, Li H, Zhang X, et al. Optimal waist circumference cutoffs for abdominal obesity in Chinese. Atherosclerosis. 2008 Dec;201(2):378–84.
18 Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi. 2007 May;35(5):390–419.
19 Kong X, Xing X, Hong J, Zhang X, Yang W. Association of a type 2 diabetes genetic risk score with insulin secretion modulated by insulin sensitivity among Chinese Hans. Clin Genet. 2017 Jun;91(6):832–42.
20 Benzinou M, Creemers JW, Choquet H, Lobbens S, Dina C, Durand E, et al. Common nonsynonymous variants in PCSK1 confer risk of obesity. Nat Genet. 2008 Aug;40(8):943–5.
21 Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet. 2008 Jun;40(6):716–8.
22 Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007 Nov;318(5855):1469–72.
23 Heard-Costa NL, Zillikens MC, Monda KL, Johansson A, Harris TB, Fu M, et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 2009 Jun;5(6):e1000539.
24 Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L, et al.; Wellcome Trust Case Control Consortium; Procardis Consortia; Giant Consortium. Genome-wide association scan meta-analysis identifies three loci influencing adiposity and fat distribution. PLoS Genet. 2009 Jun;5(6):e1000508.
25 Liu YJ, Liu XG, Wang L, Dina C, Yan H, Liu JF, et al. Genome-wide association scans identified CTNNBL1 as a novel gene for obesity. Hum Mol Genet. 2008 Jun;17(12):1803–13.
26 Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, et al.; Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; KORA; Nurses' Health Study; Diabetes Genetics Initiative; SardiNIA Study; Wellcome Trust Case Control Consortium; FUSION. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet. 2008 Jun;40(6):768–75.
27 Meyre D, Delplanque J, Chèvre JC, Lecoeur C, Lobbens S, Gallina S, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat Genet. 2009 Feb;41(2):157–9.
28 Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 2007 Jul;3(7):e115.
29 Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet. 2009 Jan;41(1):18–24.
30 Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al.; Genetic Investigation of ANthropometric Traits Consortium. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009 Jan;41(1):25–34.
31 Kim M, Jeong S, Yoo HJ, An H, Jee SH, Lee JH. Newly identified set of obesity-related genotypes and abdominal fat influence the risk of insulin resistance in a Korean population. Clin Genet. 2019 Apr;95(4):488–95.
32 Moon JY, Wang T, Sofer T, North KE, Isasi CR, Cai J, et al. Objectively Measured Physical Activity, Sedentary Behavior, and Genetic Predisposition to Obesity in U.S. Hispanics/Latinos: Results From the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Diabetes. 2017 Dec;66(12):3001–12.
33 Klimentidis YC, Wineinger NE, Vazquez AI, de Los Campos G. Multiple metabolic genetic risk scores and type 2 diabetes risk in three racial/ethnic groups. J Clin Endocrinol Metab. 2014 Sep;99(9):E1814–8.
34 Nedungadi TP, Clegg DJ. Sexual dimorphism in body fat distribution and risk for cardiovascular diseases. J Cardiovasc Transl Res. 2009 Sep;2(3):321–7.
35 Luo J, Hendryx M, Laddu D, Phillips LS, Chlebowski R, LeBlanc ES, et al. Racial and Ethnic Differences in Anthropometric Measures as Risk Factors for Diabetes. Diabetes Care. 2019 Jan;42(1):126–133.
36 Hou X, Chen S, Hu G, Chen P, Wu J, Ma X, et al.; China National Diabetes, Metabolic Disorders Study Group. Stronger associations of waist circumference and waist-to-height ratio with diabetes than BMI in Chinese adults. Diabetes Res Clin Pract. 2019 Jan;147:9–18.
37 Li S, Xiao J, Ji L, Weng J, Jia W, Lu J, et al.; China National Diabetes and Metabolic Disorders Study Investigators. BMI and waist circumference are associated with impaired glucose metabolism and type 2 diabetes in normal weight Chinese adults. J Diabetes Complications. 2014 Jul-Aug;28(4):470–6.
38 Lim RB, Chen C, Naidoo N, Gay G, Tang WE, Seah D, et al. Anthropometrics indices of obesity, and all-cause and cardiovascular disease-related mortality, in an Asian cohort with type 2 diabetes mellitus. Diabetes Metab. 2015 Sep;41(4):291–300.
39 Czernichow S, Kengne AP, Huxley RR, Batty GD, de Galan B, Grobbee D, et al.; ADVANCE Collaborative Group. Comparison of waist-to-hip ratio and other obesity indices as predictors of cardiovascular disease risk in people with type-2 diabetes: a prospective cohort study from ADVANCE. Eur J Cardiovasc Prev Rehabil. 2011 Apr;18(2):312–9.
40 Ahmad S, Zhao W, Renström F, Rasheed A, Samuel M, Zaidi M, et al. Physical activity, smoking, and genetic predisposition to obesity in people from Pakistan: the PROMIS study. BMC Med Genet. 2015 Dec;16(1):114.

Obes Facts 2019;12:328–343
DOI: 10.1159/000500490

41 Fesinmeyer MD, North KE, Lim U, Bůžková P, Crawford DC, Haessler J, et al. Effects of smoking on the genetic risk of obesity: the population architecture using genomics and epidemiology study. BMC Med Genet. 2013 Jan;14(1):6.
42 Ahmad S, Rukh G, Varga TV, Ali A, Kurbasic A, Shungin D, et al.; InterAct Consortium; DIRECT Consortium. Gene × physical activity interactions in obesity: combined analysis of 111,421 individuals of European ancestry. PLoS Genet. 2013;9(7):e1003607.
43 Zou X, Zhou X, Ji L, Yang W, Lu J, Weng J, et al. The characteristics of newly diagnosed adult early-onset diabetes: a population-based cross-sectional study. Sci Rep. 2017 Apr;7(1):46534.
44 Hales CM, Fryar CD, Carroll MD, Freedman DS, Aoki Y, Ogden CL. Differences in Obesity Prevalence by Demographic Characteristics and Urbanization Level Among Adults in the United States, 2013-2016. JAMA. 2018 Jun;319(23):2419–29.
45 Ramachandran A, Chamukuttan S, Shetty SA, Arun N, Susairaj P. Obesity in Asia: is it different from rest of the world. Diabetes Metab Res Rev. 2012 Dec;28 Suppl 2:47–51.
46 Rotter I, Rył A, Grzesiak K, Szylińska A, Pawlukowska W, Lubkowska A, et al. Cross-Sectional Inverse Associations of Obesity and Fat Accumulation Indicators with Testosterone in Non-Diabetic Aging Men. Int J Environ Res Public Health. 2018 Jun;15(6):E1207.
47 Shi H, Seeley RJ, Clegg DJ. Sexual differences in the control of energy homeostasis. Front Neuroendocrinol. 2009 Aug;30(3):396–404.