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Single nucleotide polymorphisms (SNPs) that are associated with obesity and type 2 diabetes among Asians: a systematic review and meta-analysis

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Single nucleotide polymorphisms (SNPs) could increase the susceptibility of individuals to develop obesity and type 2 diabetes (T2DM). Obesity and T2DM are closely related pathophysiologically, thus similar SNPs could mediate both these diseases, but this is rarely reported. Furthermore, limited studies have been performed to summarize SNP data in the Asian population compared to the Western population. In this study, we aimed to summarize SNPs that are associated with the development of obesity and T2DM among Asian populations. We searched six literature databases and Review Manager (RevMan) was used for meta-analysis. The pooled odds ratios (ORs) and 95% CIs were calculated with a random effects model for the heterogeneity among studies. The pooled analysis showed that rs9939609 (FTO gene) and rs17782313 and rs571312 (MC4R gene) are associated with obesity with an odd ratio (OR) of 1.37, 1.36 and 1.29 respectively. For T2DM, five SNPs, rs7903146 and rs12255372 (TCF7L2 gene), rs13266634 and rs11558471 (SLC30A8 gene) and rs2283228 (KCNQ1 gene) have also shown strong associations with T2DM at OR of 1.64, 1.61, 1.22, 1.29 and 1.60 respectively. This data could be used to develop a gene screening panel for assessing obesity and T2DM susceptibility.

Keywords Type 2 diabetes, Obesity, SNPs, Asian, Gene

List of symbols

%	Percent
<	Smaller than
>	Greater than
≥	Greater than and equal to
β	Beta
α	Alpha
γ	Gamma

Over the past years, non-communicable diseases (NCDs) have led to substantial mortality and morbidity globally. According to the World Health Organization, non-communicable diseases (NCDs) cause 71% of all deaths worldwide[1]. An understanding of the pathogenesis of NCDs such as obesity and Type 2 Diabetes (T2DM) is important to know the risk factors of the diseases and to ensure proper preventive measures can be taken to reduce the mortality due to NCDs[2,3]. Obesity is a condition where excessive fat accumulation occurs in the body[4] whereas T2DM is a condition where lesser insulin is secretion by pancreatic β-cells with diminished insulin efficacy in target tissues[5]. By sharing strong genetic and environmental aspects in their pathogenesis,

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obesity increases the impact of genetic susceptibility and environmental factors on T2DM. Once obesogenic and diabetogenic environmental factors amplify genetic susceptibilities, ectopic adipose tissue expansion and excessive accumulation of certain nutrients and metabolites sabotage metabolic balance. Processes including insulin resistance, dysfunctional autophagy, and the microbiome-gut-brain axis will be activated to exacerbate immunometabolism dysregulation through systemic inflammation, leading to accelerated loss of β-cell function and gradual elevation of blood glucose level[6–10].

The role of SNP in obesity and T2DM is not very straightforward due to the involvement of multiple genes in their pathogenesis. Some of these SNPs, when found in isolation, do not confer any added risks for obesity[10–12]. However, when combined, these SNPs increase obesity risk. For example, rs1801282 of the peroxisome proliferator-activated receptor γ2 (PPARγ2) gene had no significant association with obesity (OR 0.837; 95% CI 0.485–1.443) among Taiwanese until it was found in combination with SDC3 rs2282440 (combined OR 6.77; 95% CI 1.87–24.54)[11]. This showed a significant association with obesity when combined, suggesting gene–gene interactions are at play.

To date, many genetic variants that are associated with the development of obesity and T2DM have been identified through genome-wide association studies (GWAS), mostly conducted in European Descendants and some Asian populations[13,14]. However, many common genetic variants that are associated with NCDs in Europeans have not been observed in Asian populations due to differences in biological traits, cultural practices, and lifestyle habits[15,16]. For example, SNPs G2548A, H1328080, and A19G of the leptin gene are associated with obesity among Malays in the Malaysian population, only SNP G2548A is associated with obesity among Tunisian and none of these SNPs was associated with obesity among the Turkish Population[15–17]. For T2DM, three SNPs namely rs2028299 of adaptor-related protein complex 3 subunit sigma 2 (AP3S2) gene, rs3923113 of growth factor receptor-bound protein 14 (GRB14) gene and rs4812829 of hepatocyte nuclear factor 4α (HNF4α) gene are associated with increased risk of T2DM among the South Asian population whereas these effects are not observed in white Europeans[14,18]. Thus, genetic variants vary according to nativity which means populations within the same continental group evince the same allele enrichment or depletion patterns compared to inter-continental populations which show distinct patterns[19]. As a result, the identification of genes and SNPs that are involved in the pathogenesis of T2DM and obesity across a different population is important as it can affect the diagnosis, treatment, and prevention of the disease across a different population[20]. Therefore, this systematic review and meta-analysis is conducted to investigate single nucleotide polymorphisms (SNPs) in candidate genes associated with the development of obesity and T2DM across different ethnic groups in Asian populations.

Results

Systematic review of search results and risk of bias within the studies

The initial database search identified 11,860 articles from Ovid/Embase, Scopus, and the Cochrane, PubMed, Web of Science, and Science Direct databases (Fig. 1). After screening abstracts and titles, 98 articles were screened upon removal of 630 duplicates. During the second screening step for full-text articles, 90 articles related to the study area were selected. After excluding 36 articles with reasons, 54 qualified articles were included in this systematic review that was conducted in 14 different Asian countries. Of the included articles, 49 (90.74%) had case–control studies and 5 (9.26%) were cross-sectional designs. The included studies were case–control studies and cross-sectional studies in which the total number of cases and controls in the included studies was 58,601. The number of captured SNPs was 76, which mapped onto 41 different genes.

The assessment of the ROBINS-I tool is shown in Supplementary Table S1 and Supplementary Fig. S1. Based on the ROBINS-I tool, 25 studies were identified as "low risk", 9 studies were assessed as "moderate risk" studies, and 3 studies were considered as "Serious risk". Due to the distinctiveness of data extracted from each study, assessments of certainty and sensitivity analysis could not be completed.

SNPs in the Asian obesity population

From the included studies, 38 SNPs were significantly associated with obesity. The SNPs for FTO gene were most frequently reported for association with obesity compared to the other genes with 10 reported FTO SNPs (refer to Table 1). rs9939609 FTO was most reported, as supported in 5 studies[25–29]. The next frequently reported SNPs belonged to the leptin gene with 7 different SNPs reported in 6 studies[15,33,39,42]. The melanocortin-4-receptor gene (MC4R) gene with 5 different SNPs was reported in 4 studies[26,37–39]. The adiponectin gene (ADIPOQ) reported 4 SNPs[33,35,36]. Lastly, brain-derived neurotrophic factor gene (BDNF), Syndecan 3 gene (SDC3), beta-2 adrenergic receptor gene (ADRB2), TCF7L2 gene, glucagon-like peptide-1 receptor gene (GLP1R), CDK5 regulatory subunit associated protein 1 like 1 gene (CDKAL1), TMEM18 gene, fas apoptotic inhibitory molecule gene (FAIM2), nuclear receptor coactivator 2 (NCOA2) and GA binding protein transcription factor subunit beta 1 gene (GABPB1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 gene (ENPP1), Cholesterol ester transfer protein gene (CETP) and combined genotypes of FTO and TCF7L2 reported one SNP each respectively[11,30,31,33,34,40,41,41–45]. Detailed information on participants' recruitment countries is available in Supplementary Table 1.

SNPs in the Asian T2DM population

A total of 55 SNPs were captured across 36 different genes that were significantly associated with T2DM (refer to Table 2). Alike obesity SNP rs9939609 of the FTO gene, SNP rs266729 of the ADIPOQ gene, SNP rs12970134 of the MC4R gene, SNP rs6548238 of the TMEM18 gene, SNP rs7754840 of CDKAL1 and SNP rs7138803 of FAIM2 gene were also reported among T2DM Asian population[35,44,46–50,59,62]. The FTO gene and TCF7L2 gene reported four SNPs respectively[46–56] whereas SLC30A8 gene, insulin-like growth factor 2 mRNA binding protein

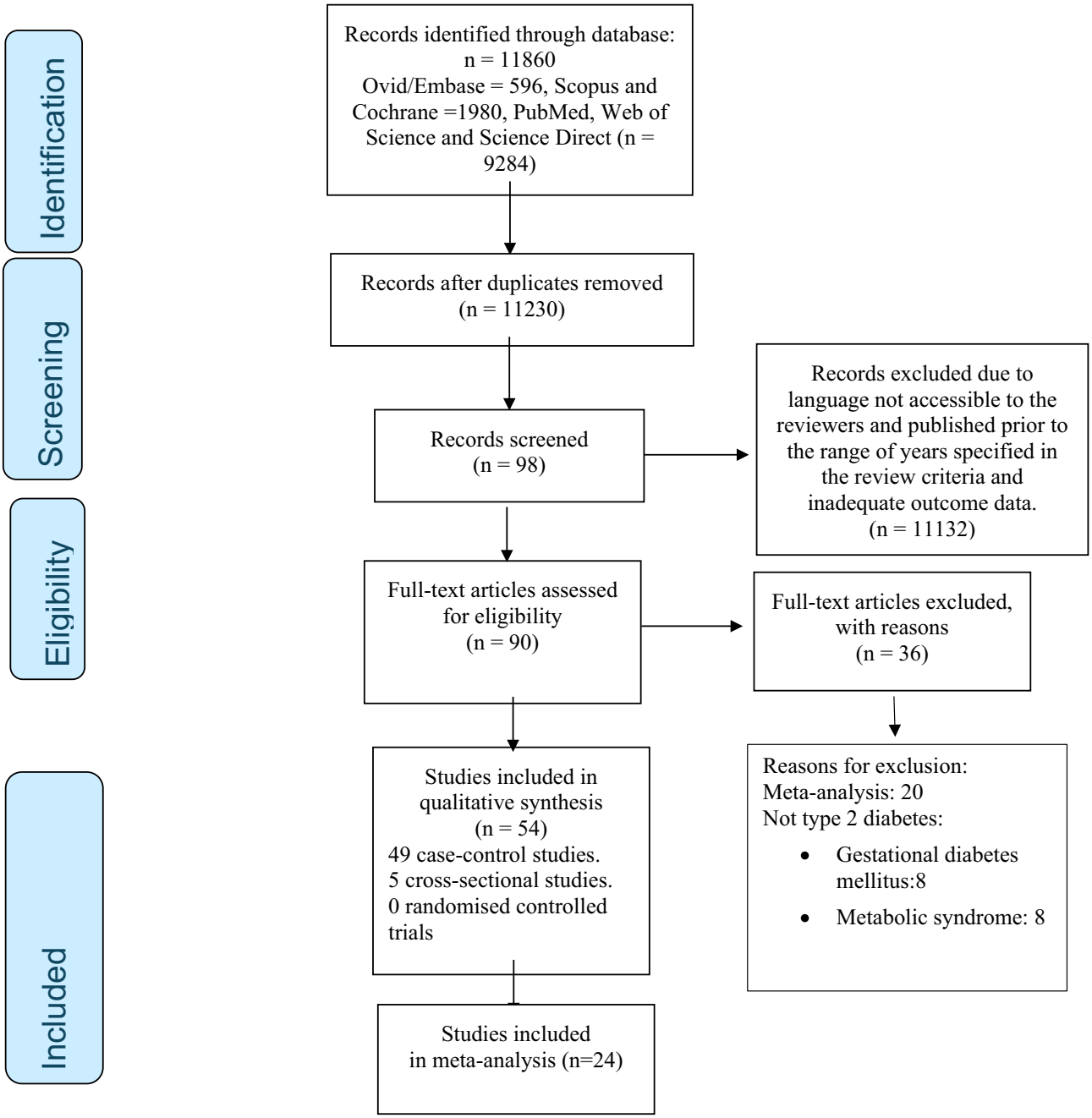

Fig. 1. PRISMA flow diagram of study selection process.

2-gene (IGF2BP2), CDKAL1 gene, haematopoietically expressed homeobox gene (HHEX) and KCNQ1 gene reported three SNPs respectively[52,54,55,57–61,64,70].

Two SNPs from the ADIPOQ gene and BDNF gene were associated with T2DM[35,46,62,63,65]. One SNP was also reported for each of the following genes for increased risk of T2D in various Asian ethnicities: sarcoglycan gamma gene (SGCG), PPARγ2 gene, MC4R gene, glucokinase (GCK), adenylate cyclase type 5 gene (ADCY5), cyclin dependent kinase inhibitor 2b gene (CDKN2B), plexin A4 gene (PLXNA4), FAIM2 gene, glucosamine-6-phosphate deaminase 2 gene (GNPDA2), bicoid interacting 3 domain-containing rna methyltransferase- fas apoptotic inhibitory molecule gene (BCDIN3D-FAIM2), tumour protein p53-inducible nuclear protein 1 gene (TP53INP1), CDKN2A/2B, melatonin receptor 1b (MTNR1B), ENPP1 gene, protein tyrosine phosphatase receptor type D gene (PTPRD), glutathione s-transferase theta 1 gene (GSTT1), glutathione s-transferase mu 1 gene (GSTM1), glutathione s-transferase pi 1 gene (GSTP1), angiotensin I converting enzyme gene (ACE), rho GTPase activating protein 22 gene (ARHGAP22), signal transducer and activator of transcription 4 gene (STAT4), ADP ribosylation factor like GTPase 15 gene (ARL15), dipeptidyl peptidase-4 (DPP-IV), ankyrin repeat and PH domain 1(ARAP1) and aquaporin-7 gene (AQP7)[46,49,50,54,55,57,66–69,71–76]. Detailed information on participants' recruitment countries is available in Supplementary Table 2.

Gene	SNP	Study design	No. of participants		Age (years)	Obesity criteria	OR	95% CI	Reference
			Cases	Control					
FTO	rs9939609	Case–control	674	214	41.6 ± 17.6	Based on WHO standards	1.47	1.01–2.12	[25]
FTO	rs9939609	Case–control	1151	1200	50–70	BMI ≥ 28 kg/m^2, according to the Chinese criteria and the waist circumferences WC ≥ 90 cm in men and ≥ 80 cm in women were defined as central obesity	1.92	1.81–4.67	[26]
FTO	rs9939609	Case–control	346	285	40.63 ± 15.19	BMI > 30 kg/m^2 and waist to hip ratio (WHR) ≥ 0.85 for women and ≥ 1 for men	2.36	1.14–4.86	[27]
FTO	rs9939609	Case–control	40	40	19–59	IOTF definitions for Asian obesity (≥ 25 kg/m^2)	3.72	1.19–11.64	[28]
FTO	rs9939609	Case–control	927	1527	49.1 ± 14.2	Based on WHO standards	1.38	1.20–1.59	[29]
FTO	rs9930506	Cross-sectional	79	99	45.3 ± 1.7	BMI ≥ 27 kg/m^2	2.87	1.14–7.19	[30]
FTO	rs3751812	Case–control	236	92	18–30	Based on WHO standards	1.52	1.08–2.15	[31]
FTO	rs8050136	Case–control	346	285	40.63 ± 15.19	BMI) > 30 kg/m^2 and waist to hip ratio (WHR) ≥ 0.85 for women and ≥ 1 in men	1.78	1.11–2.85	[27]
FTO	rs1121980						3.68	1.72–7.89	
FTO	rs9926289						2.23	1.16–4.30	
FTO	rs1558902	Case–control	927	1527	49.1 ± 14.2	Based on WHO standards	1.41	1.22–1.62	[29]
FTO	rs1121980						1.33	1.16–1.52	
FTO	rs8050136	Case–control	851	1001	51 ± 141	Based on WHO standards	1.09	0.83–1.42	[32]
FTO	rs9941349	Case–control	1000	1000	35.51 ± 10.98	Based on WHO standards	0.68	0.61–0.77	[33]
combined genotypes of FTO and TCF7L2	combined genotypes of rs9939609 and rs7903146	Case–control	240	240	20–42	Based on WHO standards	15.92	7.7–34.25	[34]
ADIPOQ	rs266729	Case–control	388	659	50.3 ± 15.1	BMI ≥ 27 kg/m^2	1.19	0.70–2.03	[35]
ADIPOQ	rs822396	Case–control	250	300	37.85 ± 9.767	Generalized obesity was defined as BMI ≥ 25	1.46	0.97–1.98	[36]
ADIPOQ	rs1501299						1.65	0.85–1.99	
ADIPOQ	rs2241766	Case–control	1000	1000	35.51 ± 10.98	Based on WHO standards	2.50	3.1–5.40	[33]
MC4R	rs17782313	Case–control	1151	1200	50–70	BMI ≥ 28 kg/m^2, according to the Chinese criteria and the waist circumferences WC ≥ 90 cm in men and ≥ 80 cm in women were defined as central obesity	1.87	1.72–4.00	[26]
MC4R	rs17782313	Cross-sectional	1250		65.9 ± 13.0	BMI ≥ 25 kg/m^2	1.3	1.0–1.8	[37]
MC4R	rs17782313	Case–control	496	604	47.7 ± 12.5	BMI > 30 kg/m^2	1.41	1.06–1.67	[38]
MC4R	rs2331841						1.49	1.14–1.96	
MC4R	rs6567160						1.45	1.09–1.92	
MC4R	rs571312						1.36	0.98–1.89	
MC4R	rs571312	Case–control	333	338	39.65 ± 10.25	IOTF definitions for Asian obesity (≥ 25 kg/m^2)	1.88	1.18–2.97	[39]
MC4R	rs12970134						1.85	1.14–2.98	
MC4R	rs12970134	Case–control	496	604	47.7 ± 12.5	BMI > 30 kg/m^2	1.37	0.97–1.92	[38]
NCOA2	rs10504473	Cross-sectional	529		58.93 ± 9.73	BMI ≥ 28 kg/m^2	1.87	1.02–3.44	[40]
GABPB1	rs7181866	Case–control	186	116	50.1 ± 9.6	Based on WHO standards	2.04	1.29–3.22	[41]
Leptin	G2548A	Case–control	148	101	18–59	Based on WHO standards	1.07	0.72–1.56	[15]
Leptin	H1328080						1.13	0.74–1.72	
Leptin	A19G						1.19	0.80–1.78	
Leptin	rs7799039	Case–control	1000	1000	35.51 ± 10.98	Based on WHO standards	0.69	0.63–0.76	[33]
Leptin	rs7799039	Case–control	333	338	39.65 ± 10.25	IOTF definitions for Asian obesity (≥ 25 kg/m^2)	2.24	1.37–3.66	[39]
Leptin	rs1137101	Case–control	1000	1000	35.51 ± 10.98	Based on WHO standards	4.42	2.76–7.08	[33]
Leptin	Gln223Arg	Case–control	250	225	39.63 ± 15.19	IOTF definitions for Asian obesity (≥ 25 kg/m^2)	2.61	1.49 to 4.59	[42]
Leptin	rs2167270	Case–control	333	338	39.65 ± 10.25	IOTF definitions for Asian obesity (≥ 25 kg/m^2)	2.24	1.30–3.87	[39]
SDC3	rs2282440	Cross-sectional	264	323	40.06 ± 11.01	BMI ≥ 27 kg/m^2	2.016	1.22–3.33	[11]
BDNF	rs10767664	Case–control	236	92	18–30	Based on WHO standards	1.92	1.32–2.81	[31]
ADRB2	rs1042713	Cross-sectional	79	99	45.3 ± 1.7	Based on WHO standards	1.38	0.08–23.93	[30]
TCF7L2	rs11196218	Case–control	60	69	34.37 ± 8.54	BMI ≥ 28 kg/m^2	2.54	1.21–5.35	[43]
GLP1-R	rs761386						1.61	0.77–3.39	

Continued

Gene	SNP	Study design	No. of participants		Age (years)	Obesity criteria	OR	95% CI	Reference
			Cases	Control					
TMEM18	rs6548238	Case–control	190	246	50.38 ± 14.47	Based on WHO standards	2.44	1.11–5.37	44
CDKAL1	rs7754840						1.35	0.62–2.97	
FAIM2	rs7138803						2.72	1.15–6.45	
CETP	rs3764261	Case–control	1000	1000	35.51 ± 10.98	Based on WHO standards	0.76	0.68–0.85	33
ENPP1	rs1044498	Case–control	50	50	24.66 ± 5.29	BMI ≥ 25 kg/m^2	1.70	0.60–4.50	45

Table 1. Association of Single-Nucleotide Polymorphisms (SNPs) with Obesity among Asians. WHO standards categorize BMI as underweight: < 18.5, normal: < 25, overweight: ≥ 25, and obese: ≥ 30.

Gene	SNP	Study design	No. of participants		Age (years)	Disease criteria	OR	95% CI	Reference
			Cases	Control					
FTO	rs9939609	Case–control	6781	7307	48.8 ± 12.6	HbA1c ≥ 7.0% or under treatment for type 2 diabetes	1.17	1.09 – 1.18	46
FTO	rs9939609	Case–control	98	251	55.3 ± 6.3	Based on IDF/ WHO standards	1.76	1.14–2.72	47
FTO	rs9939609	Case–control	296	198	49.58 ± 10.38	Based on IDF/ WHO standards	3.02	2.06–4.42	48
FTO	rs9939609	Case–control	518	518	52.8 ± 11.2	Based on IDF/ WHO standards	1.19	1.03–1.36	49
FTO	rs9939609	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877	35–70	FPG > 7.5 mmol/l (or 126 mg/dl) were classified as having Type 2 diabetes	1.32 1.16 1.16	1.15–1.49 0.93–1.45 1.01–1.32	50
FTO	rs9940128	Case–control	851	1001	51 ± 141	Based on WHO standards	2.04	1.42–2.94	51
FTO	rs1588413						1.86	1.18–2.92	
FTO	rs11076023						0.64	0.46–0.89	
TCF7L2	rs7903146	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.41	0.40–5.02	52
TCF7L2	rs7903146	Case–control	219	114	58.9 ± 10	Based on IDF/ WHO standards	3.34	1.99–5.60	53
TCF7L2	rs7903146	Case–control	500	500	57.2 ± 12.2	Based on ADA standards	1.7	1.06–2.72	54
TCF7L2	rs7903146	Case–control	225	231	NA	Based on the ADA standards	3.59	1.26–10.22	55
TCF7L2	rs7903146	Case–control	339	191	48.4 ± 11.2	Based on the ADA standards	1.70	1.28–2.27	56
TCF7L2	rs7903146	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877	35–70	FPG > 7.5 mmol/l (or 126 mg/dl) were classified as having Type 2 diabetes	1.21 1.08 1.37	0.93–1.49 0.70–1.68 1.21–1.53	50
TCF7L2	rs6585205	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.11	0.92–1.35	52
TCF7L2	rs7901695	Case–control	225	231	NA	Based on the ADA standards	3.76	1.98–7.14	55
TCF7L2	rs12255372	Case–control	339	191	48.4 ± 11.2	Based on the ADA standards	1.44	1.21—1.93	56
TCF7L2	rs12255372	Case–control	225	231	NA	Based on the ADA standards	2.20	0.78–6.19	55
SLC30A8	rs13266634	Case–control	3281		56.58 ± 9.88	Based on ADA standards	1.16	1.13–1.19	57
SLC30A8	rs13266634	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.31	1.11–1.53	52
SLC30A8	rs13266634	Case–control	500	500	57.2 ± 12.2	Based on ADA standards	1.86	1.19–2.90	54
SLC30A8	rs3802177	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.58	1.35–1.84	52
SLC30A8	rs11558471						1.35	1.16–1.59	
SLC30A8	rs11558471	Case–control	509	441	56 ± 9	Based on WHO standards	1.33	1.11–1.60	58
KCNQ1	rs2237892	Case–control	500	500	57.2 ± 12.2	Based on ADA standards	2.02	1.08–3.79	54
KCNQ1	rs2237892	Case–control	225	231	NA	Based on the ADA standards	2.80	0.71–11.13	55

Continued

Gene	SNP	Study design	No. of participants		Age (years)	Disease criteria	OR	95% CI	Reference
			Cases	Control					
KCNQ1	rs2237892	Case–control	222	140	59.4 ± 15.2	Based on WHO standards	4.22	1.79–9.99	59
KCNQ1	rs2237892	Case–control	300	230	49.8 ± 7.42	Based on a previous diagnosis of T2D and current use of a drug for its treatment	2	1.4–2.7	60
KCNQ1	rs2237895						1.9	1.4–2.7	
KCNQ1	rs2283228						1.9	1.4–2.5	
KCNQ1	rs2283228	Case–control	234	177	48.5 ± 7.51	Based on WHO standards	2.35	1.56–3.54	61
ADIPOQ	rs266729	Case–control	376	392	55.07 ± 11.90	Based on the ADA standards	2.17	1.11–4.26	62
ADIPOQ	rs266729	Case–control	388	659	50.3 ± 15.1	FPG > 126 mg/dl and HbA1C > 6%	0.74	0.45–1.22	35
ADIPOQ	rs17300539	Case–control	80	80	47.1 ± 15.7	FPG > 100 mg/dl for type 2 diabetes	4.67	2–10.7	63
CDKAL1	rs7754840	Case–control	140	140	48.40 ± 12.31	Based on IDF/ WHO standards	2.92	1.79–4.77	64
CDKAL1	rs10946398	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.78	1.46–2.17	52
CDKAL1	rs7756992	Case–control	222	140	59.4 ± 15.2	Based on WHO standards	2.29	1.25–4.19	59
BDNF	rs6265	Case–control	6781	7307	48.8 ± 12.6	HbA1c ≥ 7.0% or under treatment for type 2 diabetes	1.07	NA	46
BDNF	rs4074134	Case–control	2806	1113	52 ± 10	Based on IDF/ WHO standards	0.87	0.77–0.99	65
TMEM18	rs4854344	Case–control	6781	7307	48.8 ± 12.6	HbA1c ≥ 7.0% or under treatment for type 2 diabetes	1.16	NIL	46
TMEM18	rs6548238	Case–control	190	246	50.38 ± 14.47	Based on WHO standards	2.27	1.00–5.13	44
GNPDA2	rs10938397	Case–control	6781	7307	48.8 ± 12.6	HbA1c ≥ 7.0% or under treatment for type 2 diabetes	1.07	NIL	46
BCDIN3D–FAIM2	rs7138803						1.05	NIL	
MC4R	rs12970134						1.11	NIL	
MC4R	rs12970134	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877	35–70	FPG > 7.5 mmol/l (or 126 mg/dl) were classified as having Type 2 diabetes	1.19 1.17 1.28	0.97–1.41 0.96–1.44 1.12–1.44	50
HHEX	rs1111875	Case–control	1529	1439	60.2 ± 10.1	Based on IDF standards	1.43	1.08–1.89	52
HHEX	rs7923837						1.3	0.99–1.72	
HHEX	rs5015480						1.08	0.75–1.59	
TP53INP1	rs896854	Case–control	3281		56.58 ± 9.88	FPG value from 5.6 mmol/L	1.05	1.02–1.09	57
CDKN2A/2B	rs10811661	Case–control	500	500	57.2 ± 12.2	Based on ADA standards	1.65	1.01–2.71	54
MTNR1B	rs1387153						1.38	0.91–2.09	
ENPP1	rs1044498	Case–control	553	960	62.2 ± 8.9	FPG > 126 mg/dl for type 2 diabetes	1.84	1.46–2.33	66
PPARγ2	rs1801282	Case–control	518	518	52.8 ± 11.2	Based on IDF/ WHO standards	1.42	1.05–1.92	49
PPARγ2	rs1801282	Case–control	100	100	51.05	Based on IDF/ WHO standards	3.52	1.07–11.54	67
PPARγ2	rs1801282	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877	35–70	FPG > 7.5 mmol/l (or 126 mg/dl) were classified as having Type 2 diabetes	0.77 0.93 0.67	0.36–1.18 0.57–1.52 0.41–0.92	50
AQP7	rs2989924	Case–control	400	400	58.08 ± 8.45	Based on the ADA standards	1.66	1.07–2.57	68
SGCG	rs9552911	Case–control	996	976	46.1 ± 12.6	Based on WHO standards	1.058	0.91–1.23	69
PLXNA4	rs1593304						1.012	0.85–1.21	
FAIM2	rs7138803	Case–control	190	246	50.38 ± 14.47	Based on WHO standards	2.67	1.09–6.59	44
IGF2BP2	rs6769511	Case–control	1194	1274	52.49 ± 12.10	Based on WHO standards	1.19	1.04–1.35	70
IGF2BP2	rs4376068						1.16	1.02–1.32	
IGF2BP2	rs4402960						1.18	1.04–1.34	
IGF2BP2	rs4402960	Case–control	222	140	59.4 ± 15.2	Based on WHO standards	1.76	1.06–2.94	59

Continued

Gene	SNP	Study design	No. of participants		Age (years)	Disease criteria	OR	95% CI	Reference
			Cases	Control					
CDKN2B	rs10965250	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877	35–70	FPG > 7.5 mmol/l (or 126 mg/dl) were classified as having Type 2 diabetes	0.82 0.79 0.81	0.66–0.98 0.68–0.92 0.61–1.01	50
GCK	rs4607517	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877			1.25 1.58 1.01	1.01–1.49 1.29–1.94 0.78–1.25	
ADCY5	rs11708067	Case–control	Malay :722 Chinese:819 Indian: 851	Malay :882 Chinese:835 Indian: 877			0.69 N/A 0.74	0.32–1.96 N/A 0.54–0.93	
PTPRD	rs17584499	Case–control	397	285	52.0 ± 8.6	Based on WHO standards	1.42	1.04–1.95	71
GSTT1	rs17856199	Case–control	225	231	NA	Based on the ADA standards	2.16	1.39–3.36	55
GSTM1	rs366631	Case–control	225	231	NA	Based on the ADA standards	2.81	1.91–4.13	55
GSTP1	rs1695	Case–control	225	231	NA	Based on the ADA standards	3.03	1.61–5.67	55
ACE	rs4646994	Case–control	225	231	NA	Based on the ADA standards	4.19	2.36–7.44	55
ARHGAP22	rs4838605	Case–control	319	387	58.89 ± 12.01	Based on WHO standards	1.54	1.06–2.24	72
STAT4	rs3821236	Case–control	500	501	59.87 ± 12.87	FPG ≥ 7.0 mmol/L or OGTT ≥ 11.1 mmol/L or Random blood glucose ≥ 11.1 mmol/L)	1.23	1.03–1.47	73
ARL15	rs26770	Case–control	327	324	62.12 ± 6.70	Based on the ADA standards	0.71	0.44–1.14	74
DPP-IV	rs3788979	Case–control	100	100	49.33 ± 12.02	FPG ≥ 126 mg/dl or HbA1C ≥ 6.5%	4.24	1.35–3.26	75
DPP-IV	rs7608798						3.17	1.76–5.73	
ARAP1	rs1552224	Case–control	1,194	1,292	52.71 ± 10.52	Based on the ADA standards	12.07	1.58–92.34	76

Table 2. Association of Single-Nucleotide Polymorphisms (SNPs) with T2DM among Asians. WHO/IDF/ADA Diagnostic Criteria for Type 2 Diabetes: FPG ≥ 126 mg/dL (7.0 mmol/L) OR OGTT 2-h PG ≥ 200 mg/dL (11.1 mmol/L).

Meta-analyses

We first conducted a meta-analysis to analyze the association of the following SNPs with obesity, i.e. rs9939609 of the *FTO* gene and rs17782313, rs571312 and rs12970134 of the *MC4R* gene and rs7799039 of the leptin gene (refer Figs. 2, 3, 4, 5 and 6)[25–29,33,37–39]. The data from the five studies of rs9939609 of the *FTO* gene under the allelic model (A vs T) yielded a significant association with obesity (OR: 1.37; CI 1.26–1.49; $P < 0.00001$; $I^2 = 0\%$) (Fig. 2)[25–29]. Similarly, rs17782313 and rs571312 of the *MC4R* gene showed a significant association with obesity (OR: 1.36; CI 1.22–1.52; $P < 0.00001$; $I^2 = 0\%$, OR: 1.29; CI 1.11–1.51; $P = 0.001$; $I^2 = 0\%$; Figs. 3 and 4)[26,37–39]. Although both rs9939609 and rs17782313 were highly significant SNPs with very low *P*-values, rs9939609 gave a marginally higher OR indicating a stronger association with obesity.

Next, we conducted a meta-analysis to analyze the association of the following SNPs with T2DM, i.e. rs9939609 of the *FTO* gene, rs7903146 and rs12255372 of the *TCF7L2* gene, rs13266634 and rs11558471 of the *SCL30A8* gene, rs2237892 and rs2283228 of the *KCNQ1* gene, rs266729 of the *ADIPOQ* gene, rs1801282 of the *PPARγ2* gene and rs4402960 of the *IGF2BP2* gene (refer Figs. 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16)[35,47–49,52–56,58–62,67,70]. From the pooled data, only five SNPs showed a significant association with T2DM under the allelic model. The data from five studies showed that rs7903146 of the *TCF7L2* gene was significantly associated with T2DM (OR 1.64; CI 1.38–1.96; $P < 0.00001$; $I^2 = 40\%$) (Fig. 8)[52–56]; two studies similarly reported that rs12255372 of the *TCF7L2* gene was significantly associated with T2DM under the allelic model G vs T (OR 1.61; CI 1.02–2.54; $P = 0.04$; $I^2 = 77\%$) (Fig. 8)[55,56]. On the other hand, rs13266634 and rs11558471 of the *SCL30A8* gene were found to be significantly associated with T2DM (OR 1.22; CI 1.11–1.33; $P < 0.0001$; $I^2 = 0\%$, OR 1.29; CI 1.18–1.41; $P < 0.00001$; $I^2 = 0\%$) (Figs. 10 and 13)[52,54,58]. Two studies showed that rs2283228 of the *KCNQ1* gene under the allelic model C versus A was significantly associated with T2DM (OR 1.60; CI 1.31–1.96; $P < 0.00001$; $I^2 = 0\%$; Fig. 12)[60,61]. Comparing the ORs, we can conclude that rs7903146 of the *TCF7L2* gene has the strongest association with T2DM.

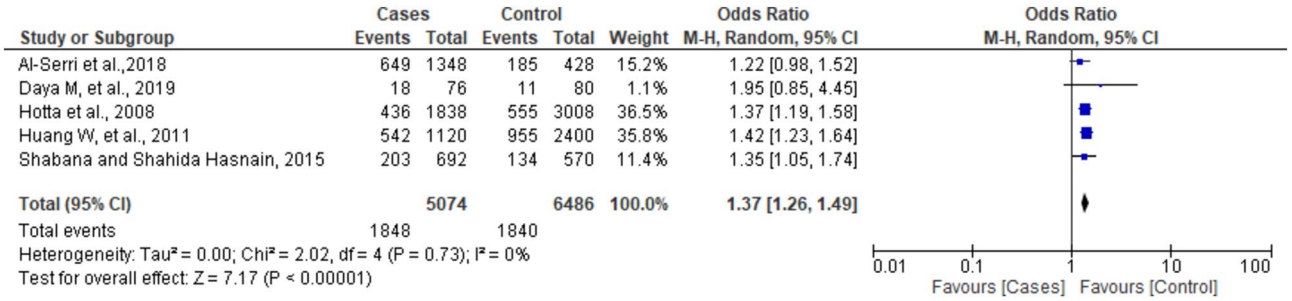

Fig. 2. Forest plot of FTO rs9939609 and obesity using the allelic model (A vs T).

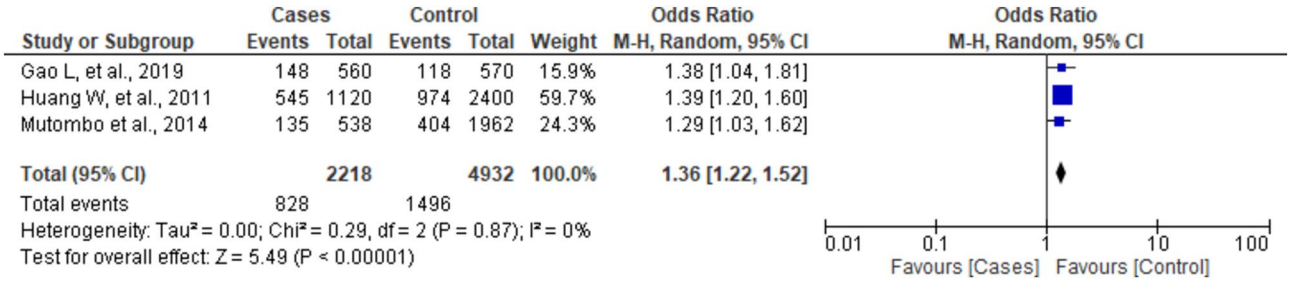

Fig. 3. Forest plot of MC4R rs17782313 and obesity using the allelic model (C vs T).

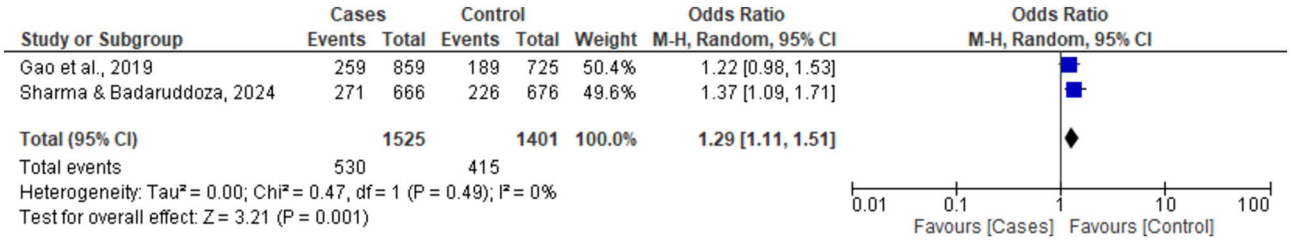

Fig. 4. Forest plot of MC4R rs571312 and obesity using the allelic model (A vs C).

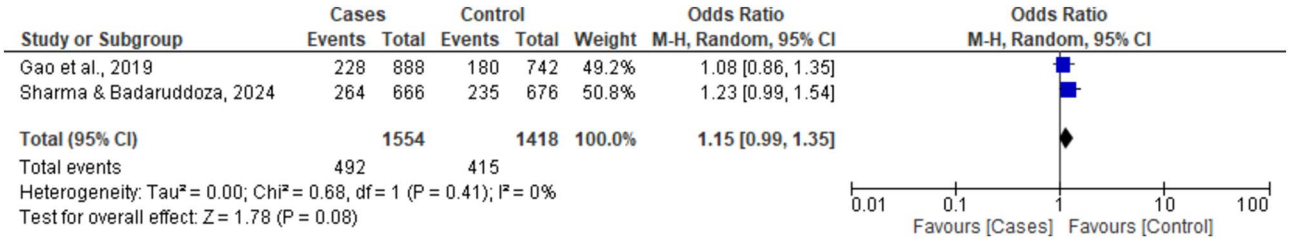

Fig. 5. Forest plot of MC4R rs12970134 and obesity using the allelic model (A vs G).

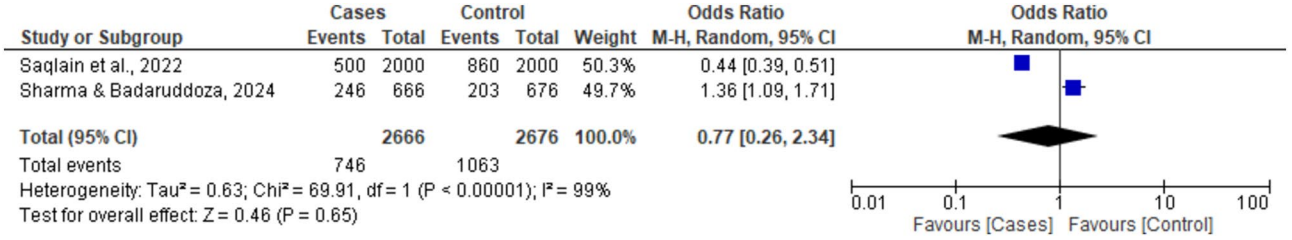

Fig. 6. Forest plot of leptin rs7799039 and obesity using the allelic model (G vs A).

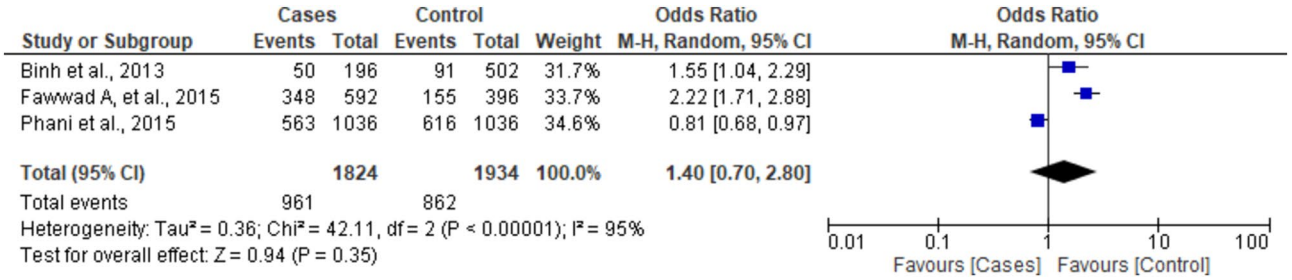

Fig. 7. Forest plot of FTO rs9939609 and T2DM using the allelic model (A vs T).

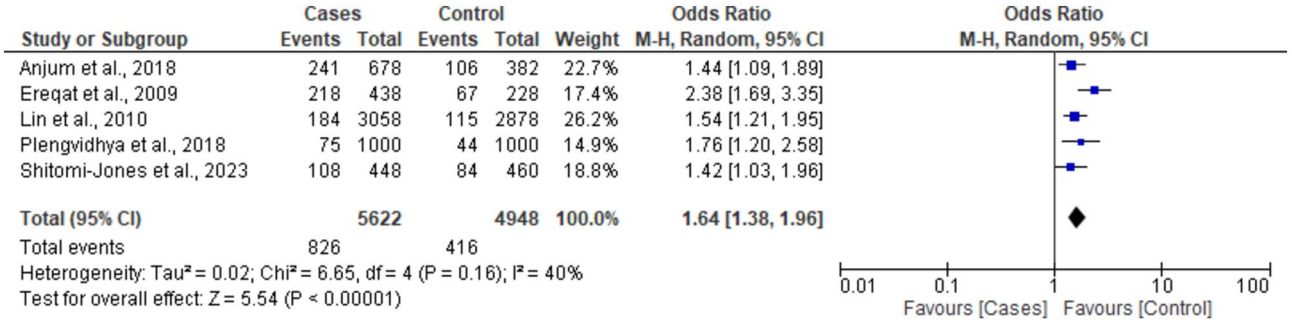

Fig. 8. Forest plot of TCF7L2 rs7903146 and T2DM using the allelic model (T vs C).

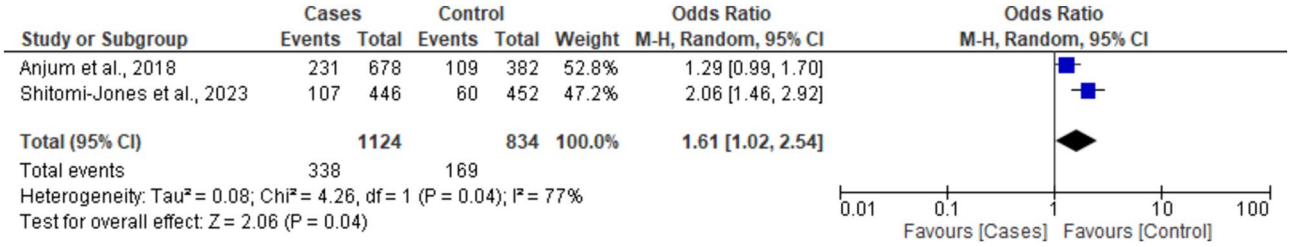

Fig. 9. Forest plot of TCF7L2 rs12255372 and T2DM using the allelic model (G vs T).

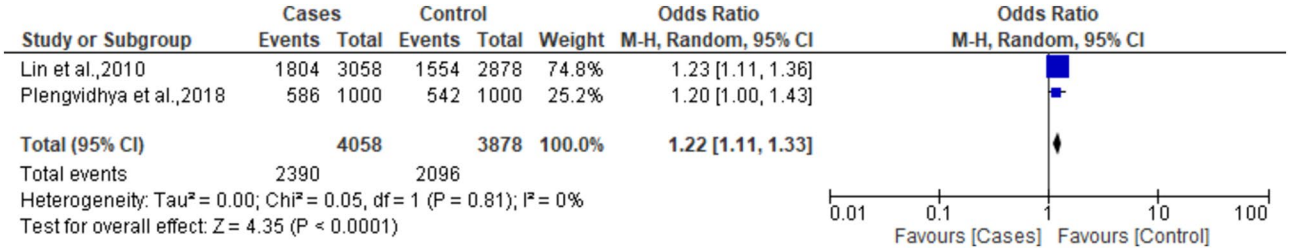

Fig. 10. Forest plot of SCL30A8 rs13266634 and T2DM using the allelic model (C vs T).

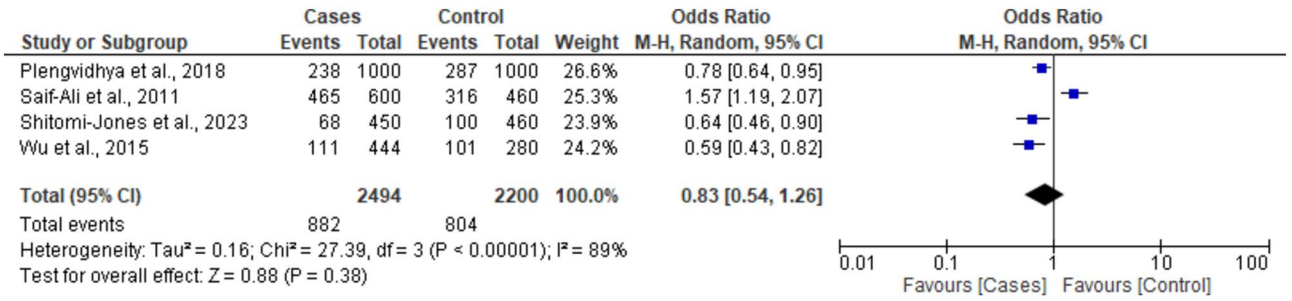

Fig. 11. Forest plot of KCNQ1 rs2237892 and T2DM using the allelic model (C vs T).

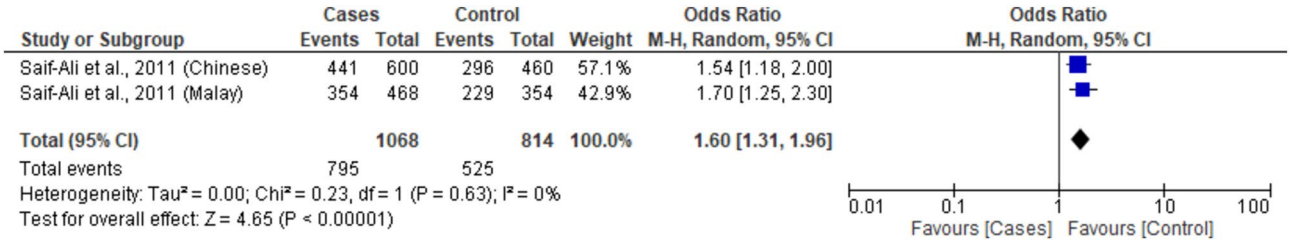

Fig. 12. Forest plot of KCNQ1 rs2283228 and T2DM using the allelic model (C vs A).

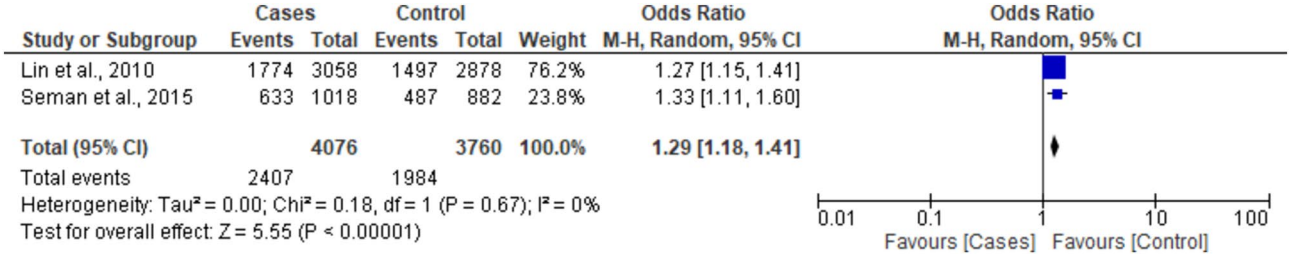

Fig. 13. Forest plot of SLC30A8 rs11558471 and T2DM using the allelic model (A vs G).

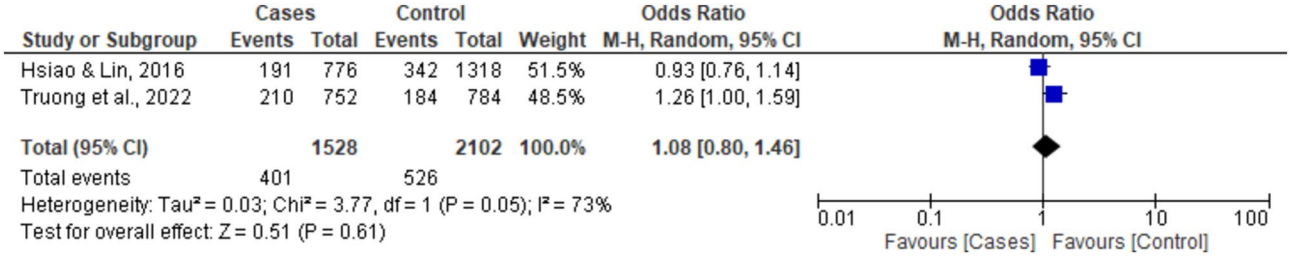

Fig. 14. Forest plot of ADIPOQ rs266729 and T2DM using the allelic model (C vs G).

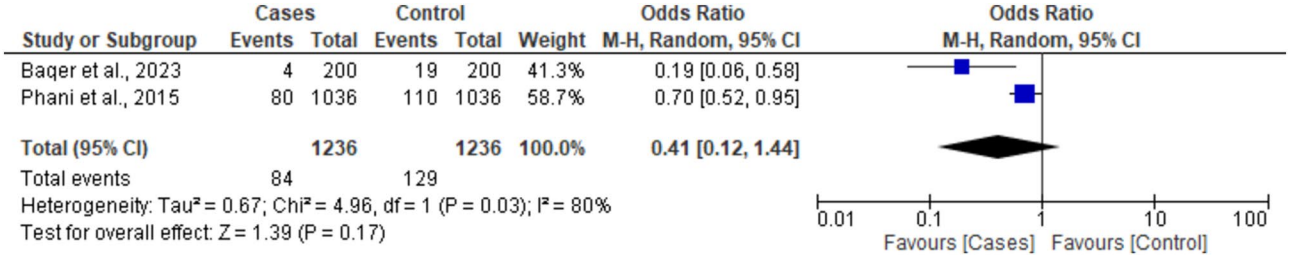

Fig. 15. Forest plot of PPARγ2 rs1801282 and T2DM using the allelic model (C vs G).

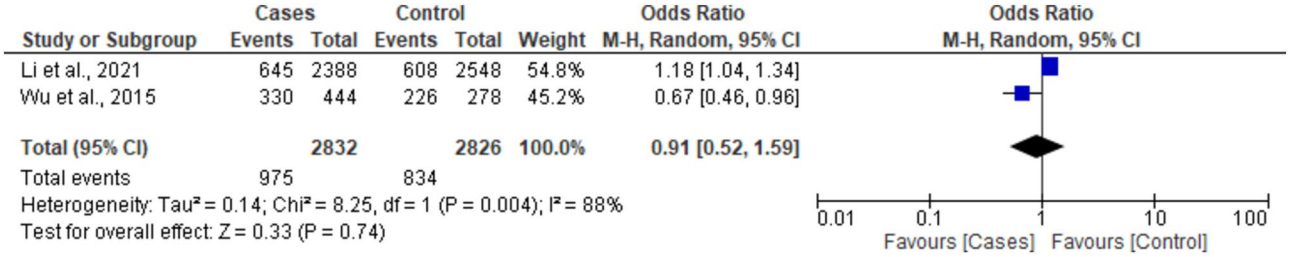

Fig. 16. Forest plot of IGF2BP2 rs4402960 and T2DM using the allelic model (G vs T).

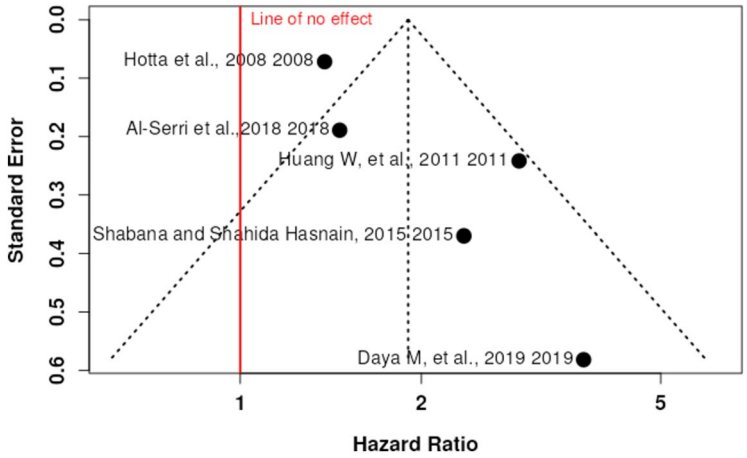

Fig. 17. Funnel plot of FTO rs9939609. The Eggers' test does not support the presence of funnel plot asymmetry (intercept: 2.19, 95% CI 0.63–3.75, t: 2.747, *P*-value: 0.071).

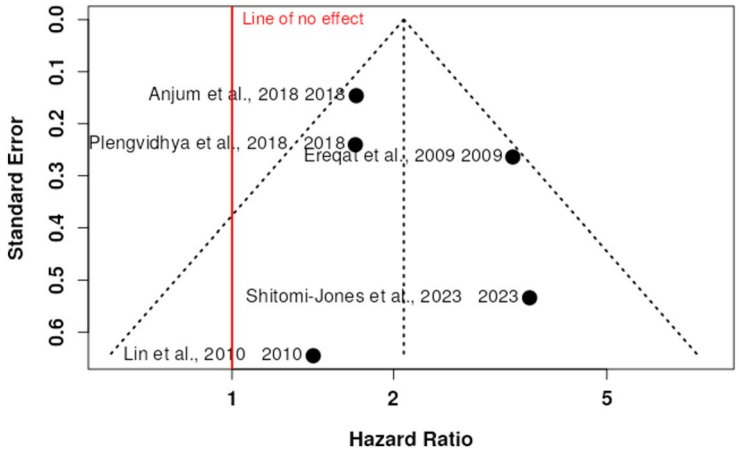

Fig. 18. Funnel plot of TCF7L2 rs7903146. The Eggers' test does not support the presence of funnel plot asymmetry (intercept: 1.03, 95% CI 1.59–3.65, t: 0.771, *P*-value: 0.497).

Publication bias

Funnel plots were constructed to assess the publication bias for two SNPs with at least five studies making the analysis feasible, namely FTO rs9939609 associated with obesity and TCF7L2 rs7903146 linked to T2DM. Neither of them showed significant publication bias (Figs. 17 and 18).

Discussion

In this study, we reviewed studies that reported the association between various SNPs of different genes with obesity and T2DM among the Asian population. Our findings indicated that FTO rs9939609 SNPs were associated with both obesity and T2DM. Other SNPs namely MC4R rs17782313 were strongly associated with obesity, whereas TCF7L2 rs7903146, KCNQ1 rs2237892 and SCL30A8 rs13266634 significantly increased the risk of T2DM development.

FTO gene is the most known gene for the predisposition of obesity as the GWAS study identified FTO as an obesity sensitivity gene, and multiple SNPs in the intron 1 region were strongly associated with BMI, body fat rate and waist and hip circumference[77]. FTO-induced obesity and increased BMI initiate the progression of T2DM. Fat cells induce insulin resistance and proinflammatory cytokine production of leptin, tumor necrosis factor and interleukin 6 to increase fasting blood glucose levels[78]. SNP rs9939609 of the FTO gene is significantly associated with both obesity and T2DM in a various population of different Asian countries. For the association of obesity, this SNP was observed among Kuwaiti, Chinese, Pakistani, Indonesian and Japanese populations with ORs ranging from 1.27 to 3.72[25–29]. Despite different risk alleles, SNP rs9939609 has a similar obesity risk among the European population proving that the FTO gene is associated with increased body weight across various populations with elevating BMI and obesity risk[79,80]. On the other hand, for T2DM, some meta-analyses that were only focused on FTO gene SNPs pooling studies reported that positive associations with rs9939609 and T2DM conducted on the East and South Asian population confirmed that there in an involvement of this SNP in

susceptibility to T2DM[81]. Furthermore, a Norwegian population-based Nord- Trøndelag Health Study (HUNT study) reported a strong association for rs9939609 with both type 2 diabetes (OR 1.13; $P = 4.5 \times 10(-8)$) and the risk of developing incident type 2 diabetes (OR 1.16; $P = 3.2 \times 10(-8)$) in Scandinavians after adjustment for age, sex and BMI giving us confidence that this gene predisposes inT2DM[82,83].

The next common gene associated with obesity risk among Asians is the MC4R gene, which regulates food intake and energy homeostasis via the hormone leptin. Among 5 reported SNPs (rs17782313, rs2331841, rs6567160, rs571312 and rs12970134), rs17782313 was captured in 3 different studies with ORs ranging from 1.3 to 1.87[27,37,38]. GWAS studies have identified that the polymorphism of rs17782313 of the MC4R gene is also associated with obesity risk among Europeans (OR 1.12; 95% CI 1.08–1.16) and this variant contributes to increased BMIs in Europeans and East Asians[33]. It is also well established that the MC4R variant CC genotype of rs17782313 is associated with a higher intake of energy and a higher percentage of energy from fatty diets[34,84].

Next, the ADIPOQ gene has been reported with 3 SNPs to be linked with obesity. GWAS has identified that SNPs of the ADIPOQ gene can decrease the serum levels of adiponectin and alter metabolic traits, such as waist-hip ratio[85]. 2 SNPs (rs822396 and rs1501299) of the ADIPOQ gene were reported among North Indian populations whereas another SNP (rs266729) was from Taipei. A case–control study conducted among South Indians replicated similar findings whereby SNPs rs822396 and rs1501299 are associated with obesity and central obesity[51]. One meta-analysis in the Chinese population found that SNPs in the ADIPOQ gene were positively linked to metabolic syndrome (which predisposes to obesity and T2D)[86]. However, there are some controversial results about ADIPOQ gene polymorphisms in the Asian population. The current understanding is that ADIPOQ SNPs alter the concentrations of adiponectin proteins, leading to metabolic changes that lead to obesity[87]. However, in Malaysian Malays, one study found no effect on adiponectin levels in individuals carrying SNPs of the ADIPOQ gene[87]. Another study found that AQIPOQ rs266729, which has previously been associated with obesity in the Indian and Thai populations, is not associated with obesity in the Taiwanese population[52,68,88].

Amongst 3 SNPs (rs7903146, rs6585205 and rs12255372) of the TCF7L2 gene, rs7903146 of the TCF7L2 gene is significantly associated with the development of T2DM among Chinese, Indian, Thai and Palestine populations with ORs ranging from (1.11–3.34). A case–control study conducted among the Thai population reported that SNP rs7903146 of the TCF7L2 gene is associated with the development of T2DM (OR 1.7 95% CI 1.06–2.72)[52]. Similarly, the risk allele T of rs7903146 was associated with T2DM in the three ethnic groups, in Caucasians (OR 1.573; 95% CI 1.100–2.250; $P = 0.0131$), African Americans (OR 2.011; 95% CI 1.265–3.196; $P = 0.003$), and Hispanics (OR 1.897; 95% CI 1.204–2.989; $P = 0.006$)[89]. This might be due to overexpression of the risk allele of the TCF7L2 gene in β cells, which results in reduced insulin secretion and causes a predisposition to T2DM directly and indirectly[90,91].

This is the first study to reveal SNPs that could increase the risk of both obesity and T2DM in the Asian population via systematic review and meta-analysis, namely FTO rs9939609. Several limitations of this study warrant consideration. Firstly, there is a potential for language bias since we have excluded articles not published in English; however, we speculate that the number is probably small and unlikely to affect our findings. Secondly, one notable limitation of this systematic review is the inability to conduct a mediation analysis. This limitation arises from the unavailability of raw data from the included studies. For mediation analysis to occur, individual-level data are required to evaluate the impact of the mediating variables between independent and dependent variables. Without access to these data, it was not possible to explore the potential pathways and mechanisms underlying the observed effects. Thirdly, the effect size was not established for the SNPs included in our review. As a result, ORs have been used as an alternative (but valid) criterion to assess the association of the SNPs with obesity and/or T2DM. Another limitation is that we were not able to examine and correct for population stratification. The absence of effect size calculation and the lack of a clear consideration of potential biases or heterogeneity in the meta-analysis might impact the robustness and interpretability of the results. Moreover, there was a lack of information such as confidence intervals (CIs), effect size and risk allele frequency (RAF) in certain articles. Finally, our meta-analysis results may be affected by the confounding factors present in the original studies where our data was taken. This is because we specifically used the allele frequencies provided for our meta-analysis, and this could explain any discrepancies found in the reported ORs between the original studies and our meta-analyses.

Conclusion

In summary, we have presented a systematic review of SNPs associated with the development of obesity and T2DM among the Asian population. From the meta-analysis we conducted to compare the individual allele effects of SNPs that were reported more than once, we found that FTO rs9939609 was the most strongly associated SNP with obesity (OR 1.37; 95% CI 1.26–1.49), while TCF7L2 rs7903146 was the most strongly associated SNP with T2D (OR 1.64; 95% CI 1.38–1.96). As T2DM and obesity are multicausal disorders, these findings can help in Asian-specific gene screening panel development for assessing obesity and T2DM susceptibility. However, large-scale genome-wide association study studies and larger population cohort studies are required in the future to further validate these SNPs candidates among Asians.

Methods

Study design

In conducting this systematic review and meta-analysis, we adhered to established guidelines to ensure methodological rigor and transparency. Specifically, we followed the preferred reporting item for systematic reviews meta-analysis (PRISMA) statement recommendation for reviewing all reported SNPs that were associated with obesity and T2DM among Asians[21]. Additionally, we adhered to the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements[22] to guide the planning, execution, and reporting of our meta-analysis.

Search strategy
An electronic literature search on peer-reviewed research articles containing case–control and cross-sectional studies published between January 2005 and April 2024 was screened to search for SNPs that were associated with obesity and T2DM among Asians. Two investigators independently identified articles (titles, abstracts, and then full texts) and screened them sequentially for inclusion criteria. We searched six literature databases: Ovid/Embase, Scopus, and the Cochrane, PubMed, Web of Science, and Science Direct databases. The search terms were "SNPs" AND "adults". Each term was used individually in combination with one of these terms: (obesity OR type 2 diabetes OR T2DM) AND (Country). For example, "SNPs" AND "adults" AND Type 2 diabetes" AND "Malaysia".

Selection criteria
Prior to the literature search, selection criteria were established to avoid selection bias. Our selection criteria included (i) articles published in English (ii) original papers containing independent data conducted in humans, (iii) research articles consisting of case–control or cross-sectional studies or randomized controlled trials, (iv) articles that only reported on Asian countries, (v) articles that contain studies that compare healthy adults and adults with obesity and/or T2DM (vi) articles with genetic variants that were associated with obesity or T2DM which reports an odds ratio (OR) and 95% confidence intervals (CIs). All articles that did not meet our inclusion criteria were excluded. Articles that were eligible for further review were identified by the authors through initial screening of the search terms. The second screening was based on a full-text review according to the selection criteria. The process of searching and selection was independently performed by two reviewers (K.Y. and J.N.Y.E) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements[21,22]. Any disagreement between the two reviewers was solved through discussion and consensus with a third reviewer (N.P.Y).

Data extraction
Information was carefully extracted from all eligible studies independently by two authors. Our search strategy resulted in 11,860 studies. Those studies were then exported to Mendeley, and 630 duplicates were detected and removed. According to our selection criteria, 54 studies were selected for further full-article screening. The selection was done by three reviewers independently to ensure that the data were captured correctly. The following information was extracted from each study: country, gene, SNPs, study design, sample size, the average age of participants, disease diagnostic standard, odds ratio (OR), 95% confidence intervals (CIs) and author and year of publication. To account for confounding factors in the studies, we used the adjusted ORs whenever provided by the original authors. For SNPs that were reported more than once, where the data was available, the allelic frequencies of the SNPs were collected as well for use in our meta-analysis.

Risk of bias
The searching and selection process was independently performed by two reviewers (K.Y. and J.N.Y.E) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Any disagreement between the two reviewers was solved through discussion and consensus with a third reviewer (N.P.Y). In addition, we used the ROBINS-I tool to evaluate the risk of bias for all the included articles from seven aspects (Supplementary Figs. 1 and 2)[23]. Two authors (K.Y. and J.N.Y.E) independently assessed the risk of bias. Any disagreement on the risk of bias score was resolved by (N.P.Y). We assessed bias due to a confounding domain according to whether the control and case groups were matched by age and gender. The biases in study participants, classification of intervention, deviations from intended interventions, and measurement of outcomes were "Low" and "Moderate". Bias due to missing data were rated whether data were reported completely. Bias in the selection of the reported result was evaluated whether the outcome was reported completely. Based on the evaluation of 7 domains, we compute the overall risk of bias and the results were reported in a rating of low, moderate, and serious[24].

Statistical analysis
Forest plots for meta-analysis were generated using ReviewManager (RevMan) 5.4.1 (The Cochrane Collaboration, Copenhagen) software. In our meta-analyses, the summary ORs and 95% CIs were calculated using the random-effects model (because the comparison of data from the three papers comparing FTO rs9939609 and T2D yields an I2 value of 95%) using the Mantel–Haenszel statistical method. To summarize study estimates (odds ratios and 95% confidence intervals) when there were two or more studies for a variant.

Data availability
All data and materials used in this review are included in the main text.

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Conceptualization, K.Y.; methodology, K.Y.; software, K.Y. and J.N.Y.E.; validation, K.Y. and J.N.Y.E.; formal analysis, K.Y. and J.N.Y.E.; data curation, writing—original draft preparation, K.Y.; writing—review and editing, K.Y., J.N.Y.E., N.P.Y., M.R.A.M., E.W.C. and A.M.N.; supervision, N.P.Y., M.R.A.M., E.W.C. and A.M.N.; funding acquisition, N.P.Y. and M.R.A.M. All authors have reviewed and agreed to the published version of the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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