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Enlightening the Correlation of Polymorphisms at *FTO*, *LEP* and *LEPR* Genes with Gestational Diabetes Mellitus Risk: a Meta-analysis

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ABSTRACT

Background: The adverse outcomes correlated with GDM for both the mother and the offspring are diverse. The link between polymorphisms at fat mass and obesity-correlated protein (FTO), leptin (LEP), and leptin receptor (LEPR) genes and GDM is ambiguous. In this meta-analysis, we sought to investigate the correlation of *FTO*, *LEP*, and *LEPR* polymorphisms with GDM risk.

Methods: We performed an online search on PubMed, Web of Science, and Google Scholar databases to identify all relevant research.

Results: A total of 18 case-control studies including seven research with 893 cases and 2875 controls on *FTO* rs9939609, four research with 1345 cases and 1116 controls on *FTO* rs8050136, two research with 207 cases and 205 controls on *FTO* rs1421085, three studies with 529 cases and 581 controls on *LEP* rs7799039, and two research with 480 cases and 477 controls on *LPER* rs1137101 met our criteria. Combined data illustrated that the *FTO* rs9939609 and rs8050136 were correlated with a substantial risk of GDM in the overall population, but not *FTO* rs1421085. Furthermore, *LEP* rs2167270 and rs7799039 polymorphisms were not correlated with GDM risk. Sorted analyses illustrated that the *FTO* rs9939609 polymorphism was correlated with GDM in Caucasian women.

Conclusion: This meta-analysis results illustrated that the *FTO* rs9939609 and rs8050136 were correlated with a substantial risk of GDM, but not *FTO* rs1421085, *LEP* rs7799039, and *LPER* rs1137101. Larger and more rigorous studies among different ethnicities are needed to further evaluate the correlations with GDM.

Introduction

Gestational diabetes mellitus (GDM) is the most frequent metabolic disease during pregnancy and is correlated with substantial maternal and neonatal morbidity.[1,2] GDM is characterized as glucose intolerance that occurs for the first time or is first identified during pregnancy.[3-5] It is well documented that GDM increases the risk of negative pregnancy outcomes and is correlated with future offspring risk of obesity and type 2 diabetes mellitus (T2DM) by epigenetic mechanisms.[6,7] GDM complexity of phenotypic outcomes might be influenced by genetic variants, nutrient-gene interactions, and lifestyle interactions with clinical factors.[8-10] The reported occurrence of GDM varies between 1 and 45% of pregnancies globally with the occurrence having substantially raised for the last decade.[11,12] In the United States, the occurrence of GDM ranges from 4 to 10%.[4,13] Nevertheless, the estimated occurrence of GDM might be affected considerably by the used data source. To date, several risk factors have been identified for GDM such as family history of GDM or T2DM, previous stillbirth, maternal age over 30-35 years, obesity, insulin resistance, maternal metabolic syndrome, ethnicity, socioeconomic status, vitamin D deficiency, and polycystic ovary disease.[14,15] It is well documented that mothers with GDM are at higher risk of gestational hypertension, cesarean delivery, and preeclampsia.[16,17]

GDM is thought to occur as a result of an autoimmune process, a condition of persistent insulin resistance, or a genetic predisposition to abnormal insulin secretion.[18,19] GDM appears to be closely related to T2DM. Thus, several T2DM-related genetic variants and epigenetic mechanisms have been assessed as potential risk factors for GDM.[6,12] Numerous genes have been implicated in the development of GDM, among them the TCF7L2, MTNR1B, CDKAL1, IRS1, and KCNQ1 genes are the most prevalent. One of the major clusters of genes that are being explored is those corresponding to modulate adiposity and obesity through several mechanisms.[12,20] Adipokines, also known as adipocytokines, are cytokines secreted by adipose tissue and involved in insulin resistance in pregnancy and GDM.[21] Three of these genes are fat mass and obesity-correlated protein (FTO), leptin (LEP), and leptin receptor (LEPR), which are correlated with body mass, obesity, and regulation of body weight in humans.[22] The human *FTO* gene is mapped on chromosome 16q12.2, contains nine exons, and encompasses 430 kb region.[23,24] *FTO* gene is vigorously conserved across different mammalian species and arose 450 million years ago.[25,26] *FTO* genetic variants have been reported to be associated with several obesity-related chronic diseases such as T2M and cancer.[27-30] Nevertheless, the link between *FTO* polymorphisms and GDM is not yet clear.[12,31] The human leptin gene is mapped on the 7q31.3 chromosome and consists of three exons.[32] Furthermore, the LEPR gene is localized on chromosome 1p31, contains 20 exons, and spans more than 70 kb.[33] Human LEP and LEPR are important regulators of the mass of adipose tissue and body weight.[32,34] LEP is effective at reducing food intake and increasing basic metabolism by binding to the hypothalamic LEPR.[32,35]

In 2009, Lauenborg et al. illustrated that the T2DM-linked loci including CDKN2A/2B, TCF7L2, CDKAL1, HHEX/IDE, FTO, IGF2BP2, TCF2, SLC30A8, PPARG, KCNJ11, and WFS1 were correlated with GDM in Danish. Their findings supported this idea that GDM and T2DM are two of the same existence.[36] In the same year, Cho et al., in a study among Korean GDM patients demonstrated that some of the T2DM-correlated genetic polymorphisms that were detected by the recent GWA research were correlated with GDM [37-39]. Since then, many researchers have assessed the correlation between *FTO* polymorphisms and GDM risk,[40,41] especially among Brazilian and European GDM patients.[21,42,43] Furthermore, some genetic variants in the *LEP* and *LEPR* gene have been

assessed as possible factors correlated with GDM.[21,35,43] Nevertheless, those research results did not demonstrate the correlation of *FTO*, *LEP*, and *LEPR* polymorphisms on GDM. Furthermore, the correlations between the polymorphisms at these genes and GDM are not certainly recognized and information in the publications is from small research in small areas of influence, with varying procedures. Therefore, we performed a meta-analysis to measure the correlation of polymorphisms occurring in the loci of the *FTO*, *LEP*, and *LEPR* genes with predisposition to GDM.

Materials and Methods

Study Selection: We performed an extensive literature review on electronic databases including PubMed, Web of Knowledge, Web of Science, WanFang, EMBASE, Scientific Information Database (SID), Chinese Biomedical Database (CBD), Scientific Electronic Library Online (SciELO), Chinese literature (Wan Fang), China National Knowledge Infrastructure (CNKI), Scopus, China Science and Technology Journal database and Egyptian Knowledge Bank (EKB) for finding all relevant researches on *FTO*, *LEP* and *LEPR* polymorphisms and, GDM published up to 30 July 2023. Furthermore, the bibliography of the literature was checked separately by two authors to find out more potentially relevant research.

Selection criteria: The inclusion criteria for this research subsisted as follows: a) research estimated the correlation between the *FTO*, *LEP*, and *LEPR* polymorphisms and GDM risk; b) case-control or cohort studies; c) studies announced allele and genotype frequency for *FTO*, *LEP* and *LEPR* polymorphisms; d) Research described in English, Persian and Chinese; e) precise data for computation of odds ratio (OR) and 95% confidence interval (CI). The exclusion criteria were as follows: a) studies did not describe the correlation of *FTO*, *LEP*, and *LEPR* polymorphisms with GDM risk; b) studies performed on animal experiments; c) case-only research or no controls; d) research that did not provide sufficient data for meta-analysis; e) linkage research and family-oriented research; f) case reports, broadsheets, commentaries, meeting abstracts, reviews, meta-analysis; and g) duplicated research.

Data Extraction: Two authors elicited data separately and the data was confirmed by the third author. The search results were then judged by four other authors. Disagreements were resolved by discussions among the reviewers. The following information was elicited from each research: first author, date of publication, country of origin, ethnic background of participants, genotyping approaches, used criteria for confirmation of GDM, source of controls, number of cases and controls for each polymorphism at *FTO*, *LEP* and *LEPR* genes, minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) in subjects. If the chosen essays did not announce the essential data, the corresponding authors were approached via email to demand the outstanding data.

Assessment of Study Quality: The quality of the chosen research was confirmed by the Newcastle-Ottawa Scale (NOS). NOS is composed of three components including a choice of attendees (four items), comparability of patients, and healthy subjects (two items), and acceptability of results (three items). It judged research with a star-rating procedure ranging from zero to nine stars, wherein scores ≥ 7 were stated high quality and ≤ 7 (insignificant risk of bias) and ≤ 7 denoted low or moderate quality (high or moderate risk of bias).

Statistical Analysis: The correlation of the *FTO*, *LEP*, and *LEPR* polymorphisms with GDM risk was assessed by computing the d by the Z-test. The correlations were computed under five genetic models: recessive (BB vs. BA+AA), dominant (BB+BA vs. AA), heterozygote (BA vs. BB), homozygote (BB vs. AA), and allelic (B vs. A). A Chi-square-based Q-test was performed to measure the heterogeneity between these researches. The

Chi-square test was used to measure the HWE of genotype distribution in healthy subjects. A Cochran's Q-test was accomplished to assess the heterogeneity and was counted as significant when $p < 0.10$. Furthermore, the I^2 value was deployed for heterogeneity confirmation. The fixed-effect model was chosen when no significant heterogeneity occurred; contrary, the random-effects model was chosen. To check the sources of heterogeneity over different researches, sorted analysis according to ethnic background, genotyping approaches, and HWE was carried out. Sensitivity analysis was done by the left-out method to examine the consequences of single research on combined results and the constancy of the outcomes. The funnel plot was appertained to appraise the publication bias. The asymmetry of the funnel plot was assessed by Egger's test. All the statistical estimates were conducted using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA).

Results

Characteristics of the Researches: As depicted by Figure 1, our initial search waived 513 studies, with duplicate research removed, resulting in 386 research left. Among these, 182 studies were excluded, established on titles and abstracts.

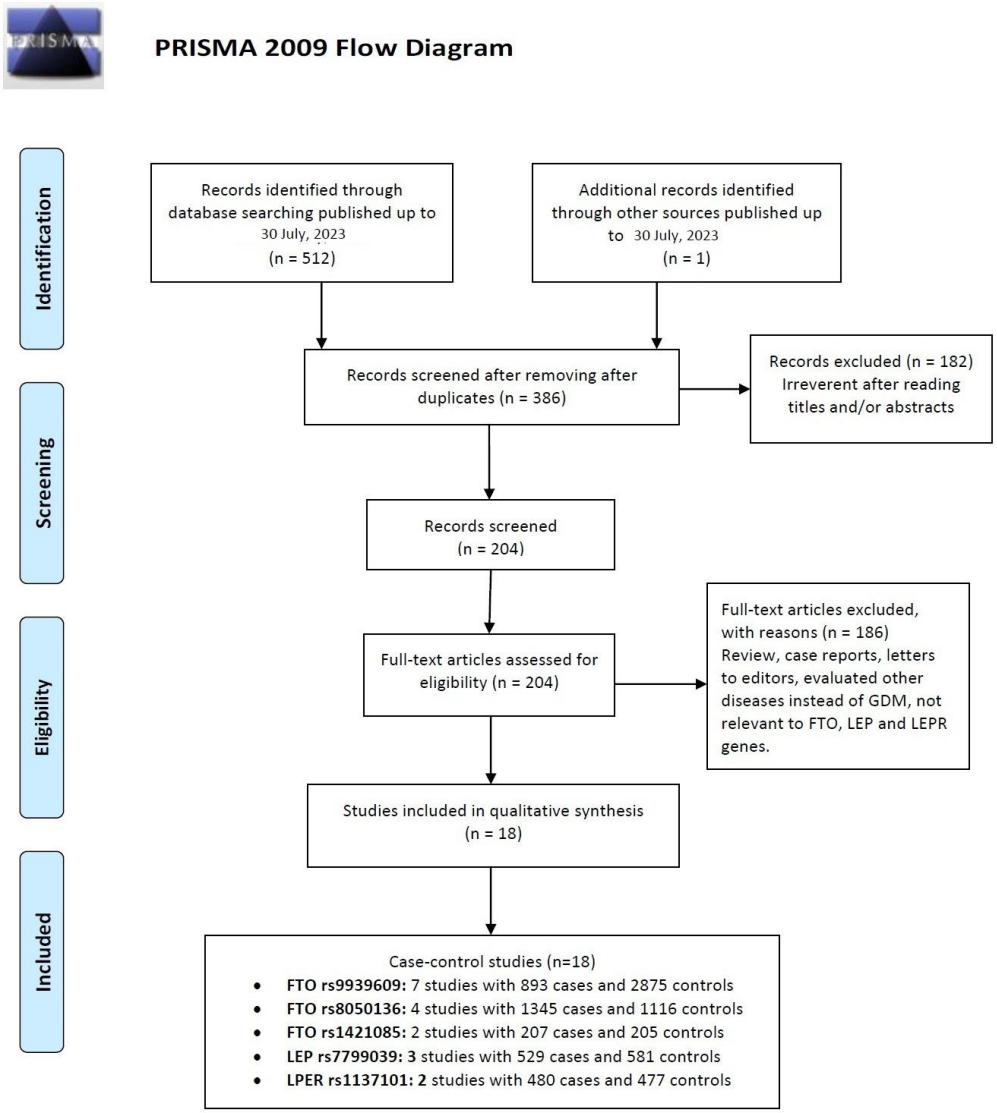

Figure 1. Flow chart for the process of selecting qualified researches

Following the inclusion-exclusion criteria, 186 studies were left out. Eventually, 18 case-control research [31,35,48,49,36,37,40,43-47] including seven research with 893 cases and 2875 controls on *FTO* rs9939609, four research with 1345 cases and 1116 controls on *FTO* rs8050136, two research with 207 cases and 205 controls on *FTO* rs1421085, three research with 529 cases and 581 controls on *LEP* rs7799039, and two research with 480 cases and 477 controls on LPER rs1137101 were chosen. Table 1 demonstrates an outline of the features of all qualified studies. GDM cases in the research ranged from 40 to 896. The chosen studies were released between June 2006 and January 2020. They have been carried out in China, Brazil, Turkey, Italy, Denmark, Poland, Spain, Czech, and Korea. Regarding ethnic background, seven research have been conducted among Caucasians, seven research among mixed populations, and four research have been conducted among Arians. Three genotyping approaches including RealTime-PCR, direct sequencing, and TaqMan were used to genotype the *FTO*, *LEP*, and *LEPR* polymorphisms. Hardy-Weinberg equilibrium (HWE) was measured for all studies, and $p < 0.05$ was considered as a departure from HWE (Table 2). The NOS score of qualified essays ranged from 6 to 7, which suggested that all inserted studies were of top quality (Table 2).

Quantitative Data Synthesis

FTO rs9939609, rs9939609 and rs1421085 Polymorphisms: The synopsis for the correlation of *FTO* rs9939609, rs9939609, and rs1421085 polymorphisms with GDM risk is displayed in Table 1. Our combined data illustrated that the *FTO* rs9939609 polymorphism was correlated with substantial risk of GDM risk under two genetic models, i.e., homozygote (AA vs. TT: OR = 1.435, 95% CI 1.111-1.852, p = 0.006, Figure 2A) and recessive (AA vs. AT+TT: OR = 1.381, 95% CI 1.251-1.880, p = 0.005, Figure 2B) in overall population. Sorted analyses by ethnic background demonstrated that the *FTO* rs9939609 polymorphism was correlated with GDM in Caucasian women under the recessive model (AA vs. AT+TT: OR = 1.470, 95% CI 1.147-1.884, p = 0.002, Figure 3), but not in mixed population (Brazilian women). As shown in Table 1, the *FTO* rs8050136 was correlated with GDM under the allele genetic model (T vs. C: OR = 0.112, 95% CI 0.016-0.766, p = 0.026, Figure 4). Nevertheless, there was not a substantial correlation by ethnic background. Furthermore, combined results demonstrated that the *FTO* rs1421085 polymorphism did not associate with GDM risk in the overall population.

***LEP* rs7799039 and *LEPR* rs1137101 Polymorphisms:** The synopsis for the correlation of the *LEP* rs7799039 and *LEPR* rs1137101 polymorphisms with GDM risk is provided in Table 3. The combined data illustrated that neither *LEP* rs7799039 nor *LEPR* rs1137101 polymorphisms were correlated with GDM risk under all five genetic models.

Test of heterogeneity: The heterogeneity in the overall population and by sorted analyses is outlined in Table 1. In this study, there was measurable heterogeneity in the overall meta-analysis for *FTO* rs9939609 (under allele and dominant models), rs8050136 (under allele), and rs1421085 (under allele, homozygote, dominant and recessive). Thus, we performed a sorted analysis by ethnic background to assess the potential source of heterogeneity under all genetic models. Results suggested that the primary factors may not assist in the ascertained heterogeneity for *FTO* rs9939609 and rs8050136 polymorphisms. There was no significant heterogeneity for *LEP* rs7799039 and *LEPR* rs1137101 variants in the overall meta-analysis.

Sensitivity analysis: The practice of carrying out combined data implies a chain of decisions, and it is essential to carry out a sensitivity analysis or the purpose of examining the impact effect of multiple factors on combined data. Thus, we performed a sensitivity analysis to measure the effect of through exclusion of a single study successively on combined data.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

First author/Year	Country (Ethnicity)	SOC	Diagnostic Criteria	Genotyping Methods	Case/Control	Cases					Controls					MAFs	HWE	NOS
						Genotypes			Alleles		Genotypes			Alleles				
FTO rs9939609						TT	TA	AA	T	A	TT	TA	AA	T	A			
Ling 2020	China (Asian)	NA	NA	PCR	40/30	20	7	3	47	13	25	5	0	55	5	0.083	0.618	5
Beysel 2019	Turkey (Caucasian)	NA	NA	RT-PCR	160/145	59	62	39	180	140	73	54	18	200	90	0.310	0.117	7
Saucedo 2017	Brazil (mixed)	HB	ADA	TaqMan	80/80	61	18	1	140	20	59	20	1	138	22	0.138	0.628	6
Franzago 2017	Italy (Caucasian)	HB	OGTT	HRM	102/66	33	39	30	105	99	16	33	17	65	67	0.508	0.998	6
de Melo 2015	Brazil (mixed)	PB	ADA	TaqMan	200/200	68	100	32	236	164	71	97	32	239	161	0.403	0.906	6
Pagan 2014	Spain (Caucasian)	HB	OM/NDDG	Sequencing	45/25	23	15	7	61	29	5	15	5	25	25	0.406	0.337	6
Lauenborg 2009	Denmark (Caucasian)	PB	OGTT	TaqMan	283/2446	82	133	61	297	255	833	1101	395	2767	1891	0.406	0.337	6
FTO rs8050136						CC	AC	AA	C	C	CC	AC	AA	C	A			
Tarnowski 2019	Poland (Caucasian)	NA	IADPSG	TaqMan	204/207	58	99	47	215	193	66	94	47	226	188	0.454	0.226	6
Saucedo 2017	Italy (Caucasian)	HB	ADA	TaqMan	80/80	61	18	1	140	20	59	20	1	138	22	0.138	0.628	6
de Melo 2015	Brazil (mixed)	PB	ADA	TaqMan	200/200	73	102	25	248	152	74	96	30	244	156	0.390	0.900	6
Cho 2009	Korea (Asian)	HB	IWCGDM	TaqMan	869/632	643	208	13	1494	234	486	132	11	1104	154	0.122	0.559	5
FTO rs1421085						TT	TC	CC	T	C	TT	TC	CC	T	C			
Saucedo 2017	Brazil (mixed)	HB	ADA	TaqMan	80/80	64	15	1	143	17	58	20	2	136	24	0.150	0.860	6
Oliveira 2017	Brazil (mixed)	HB	ADA/BDA	TaqMan	127/127	52	61	14	165	89	53	52	20	158	92	0.368	0.237	7
LEP rs7799039						GG	GA	AA	G	A	GG	GA	AA	G	A			
Teleginski 2017	Brazil (mixed)	NA	SBD	TaqMan	134/180	57	56	21	170	98	67	81	32	215	145	0.403	0.385	6
Yang 2016	China (Asian)	HB	OGTT	TaqMan	347/348	172	149	26	493	201	195	132	21	522	174	0.250	0.830	8
Vasku 2006	Czech (Caucasian)	PB	OGTT	RFLP	48/53	9	28	11	46	50	21	24	8	66	40	0.377	0.791	6
LPER rs1137101						GG	GA	AA	G	A	GG	GA	AA	G	A			
Oliveira 2017	Brazil (mixed)	HB	ADA/BDA	TaqMan	127/125	38	69	20	145	109	43	55	27	141	109	0.436	0.238	6
Yang 2016	China (Asian)	HB	OGTT	TaqMan	347/348	280	68	5	628	78	277	74	1	628	76	0.198	0.085	8

Abbreviations: HB: Hospital Based; PB: Population Based; OGTT: Oral Glucose Tolerance Test; IADPSG: International Association of Diabetes and Pregnancy Study Groups; ADA; American Diabetes Association; NDDG: National Diabetes Data Group; IWCGDM: International Workshop-Conference on Gestational Diabetes Mellitus; BDA: Brazilian Diabetes Association; OM: O'Sullivan and Mahan; NDDG: National Diabetes Data Group; HRM High-Resolution Melting; MAFs: Minor Allele Frequencies; HWE: Hardy-Weinberg Equilibrium; NOS: Newcastle-Ottawa Scale.

Table 2. Summary Risk Estimates for Association of the FTO Polymorphisms with GDM Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio(OR)				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{OR}	P_{OR}	P_{Beggs}	P_{Eggers}
FTO rs9939609										
Overall	A vs. T	Random	67.71	0.005	1.089	0.832-1.427	0.621	0.534	0.548	0.392
	AT vs. TT	Fixed	51.14	0.056	1.091	0.897-1.327	0.874	0.382	0.229	0.176
	AA vs. TT	Fixed	49.31	0.066	1.435	1.111-1.852	2.769	0.006	1.000	0.666
	AA+AT vs. TT	Random	60.82	0.018	1.059	0.751-1.494	0.329	0.742	0.367	0.150
	AA vs. AT+TT	Fixed	0.059	0.423	1.381	1.104-1.727	2.827	0.005	0.763	0.983
Ethnicity										
Caucasian	A vs. T	Random	80.44	0.002	1.049	0.694-1.583	0.226	0.821	0.308	0.346
	AT vs. TT	Random	73.65	0.010	0.844	0.476-1.497	-0.580	0.562	0.089	0.150
	AA vs. TT	Random	67.05	0.028	1.295	0.691-2.426	0.807	0.420	0.308	0.416
	AA+AT vs. TT	Random	78.02	0.003	0.961	0.540-1.712	-0.133	0.894	0.308	0.193
	AA vs. AT+TT	Fixed	13.15	0.327	1.470	1.147-1.884	3.041	0.002	0.308	0.750
Mixed	A vs. T	Fixed	0.00	0.697	1.009	0.779-1.307	0.066	0.947	NA	NA
	AT vs. TT	Fixed	0.00	0.624	1.018	0.701-1.479	0.095	0.924	NA	NA
	AA vs. TT	Fixed	0.00	0.958	1.041	0.583-1.857	0.135	0.893	NA	NA
	AA+AT vs. TT	Fixed	0.00	0.636	1.017	0.712-1.453	0.091	0.927	NA	NA
	AA vs. AT+TT	Fixed	0.00	1.000	1.000	0.592-1.691	0.00	1.000	NA	NA
FTO rs8050136										
Overall	A vs. C	Random	99.39	≤0.001	0.112	0.016-0.766	-2.232	0.026	1.000	0.891
	AC vs. CC	Fixed	0.00	0.860	1.146	0.950-1.381	1.423	0.155	0.308	0.178
	AA vs. CC	Fixed	0.00	0.904	0.979	0.683-1.403	-0.116	0.908	1.000	0.765
	AA+AC vs. CC	Fixed	0.00	0.846	1.118	0.934-1.339	1.215	0.225	0.308	0.197
	AA vs. AC+CC	Fixed	0.00	0.937	0.919	0.664-1.273	-0.506	0.613	1.000	0.808
Ethnicity									NA	NA
Caucasian	A vs. C	Fixed	98.93	≤0.001	0.132	0.004-4.039	-1.160	0.246	NA	NA
	AC vs. CC	Fixed	0.00	0.466	1.097	0.747-1.611	0.472	0.637	NA	NA
	AA vs. CC	Fixed	0.00	0.911	1.131	0.668-1.916	0.459	0.646	NA	NA
	AA+AC vs. CC	Fixed	0.00	0.483	1.909	0.759-1.570	0.471	0.637	NA	NA
	AA vs. AC+CC	Fixed	0.00	0.990	1.019	0.647-1.604	0.080	0.937	NA	NA
FTO rs1421085										
Overall	C vs. T	Random	0.00	0.374	0.878	0.638-1.207	-0.803	0.422	NA	NA
	CT vs. TT	Fixed	38.55	0.202	1.018	0.660-1.572	0.082	0.934	NA	NA
	CC vs. TT	Random	0.00	0.727	0.684	0.325-1.440	-1.001	0.317	NA	NA
	CC+CT vs. TT	Random	40.62	0.192	0.917	0.606-1.388	-0.409	0.683	NA	NA
	CC vs. CT+TT	Random	0.00	0.819	0.647	0.321-1.303	-1.219	0.223	NA	NA

NA: Not Applicable

The outcomes outlined that no individual study affected the combined results of all concerned polymorphisms at *FTO*, *LEP*, and *LEPR* genes, proposing the stability of our measurements.

Publication bias: Begg's funnel plot and Egger's test were applied to measure the kinds of literature bias for qualified studies on *FTO* (rs9939609 and rs8050136) polymorphisms and *LEPR* (rs1137101) polymorphisms. The Egger's test findings for the *FTO* and *LEPR* polymorphisms are provided in Tables 1 and 3.

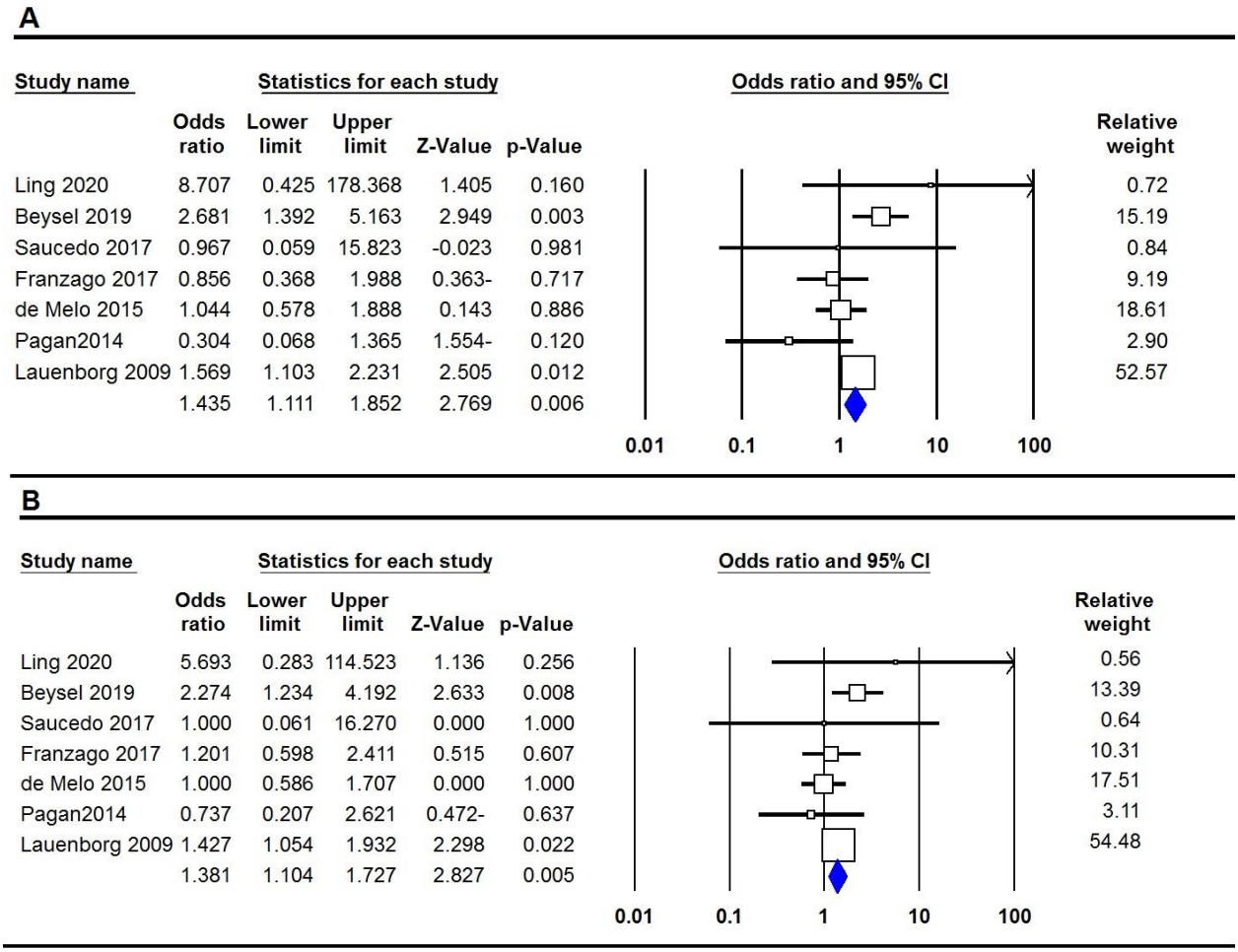

Figure 2. Forest plot for correlation between FTO rs9939609 polymorphism and GDM risk. A: allele model (A vs. T); and B: recessive model (AA vs. AT+TT)

Begg's funnel did not show a substantial literatures bias in any of the models for each variant at *FTO* and *LEPR* genes (Figure 5A-C). The constrained amount of samples is commonly accompanied by selection bias. Nevertheless, the publication bias tests exhibited that our combined ORs were faithful.

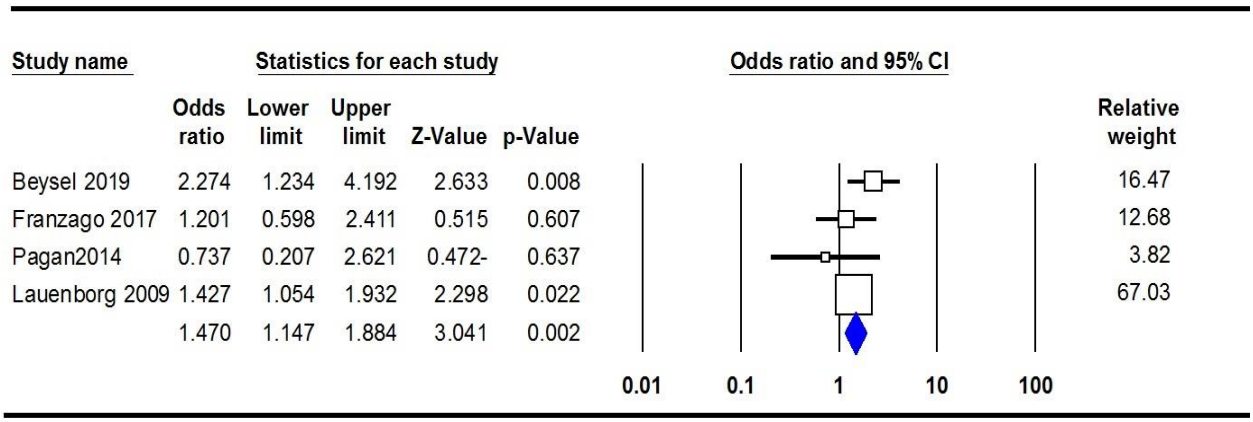

Figure 3. Forest plot for correlation between FTO rs9939609 polymorphism and GDM risk in Caucasians under recessive model (AA vs. AT+TT)

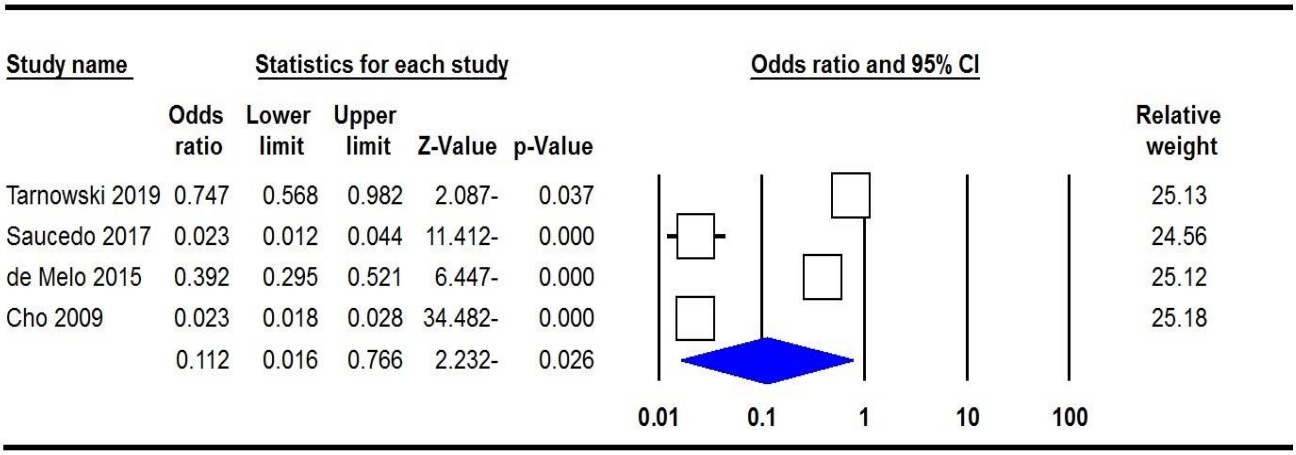

Figure 4. Forest plot for correlation between FTO rs8050136 polymorphism and GDM risk under allele model (A vs. C)

Discussion

GDM is a pregnancy disorder of carbohydrate and glucose metabolism, which is correlated with adverse maternal and perinatal outcomes.[50] The primary factors resulting in the development of GDM are complicated to ascertain and may involve a compound of diverse environmental, genetic liability, and epigenetic factors.[12] During the last two decades, several epidemiological researches have been carried out on the genetic and epigenetic etiology of GDM.[12,51,52] The *FTO* gene was previously found to be correlated with energy balance regulation and predisposition to obesity.[53,54] It is not known whether the correlation between genetic variation in the *FTO* gene and GDM is mediated through effects on energy intake and energy expenditure.[52,55,56] To date, numerous attempts have been carried out to determine genetic variants within the *FTO* gene that may be connected with GDM. Here, we performed a meta-analysis to measure the correlation of the *FTO*, *LEP*, and *LEPR* polymorphisms with GDM risk. These combined data may help knowledge of the role and mechanism of *FTO*, *LEP*, and *LEPR* genes in the pathology of GDM.

Table 3. Summary Risk Estimates for Association of the LEP and LEPR Polymorphisms with GDM Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio(OR)				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{OR}	P_{OR}	P_{Beggs}	P_{Eggers}
LEP rs7799039										
Overall	G vs. A	Fixed	65.78	0.054	1.139	0.950-1.366	1.407	0.160	0.296	0.254
	GA vs. AA	Fixed	63.16	0.066	1.196	0.928-1.541	1.384	0.166	1.000	0.760
	GG vs. AA	Fixed	56.38	0.101	1.215	0.800-1.846	0.912	0.362	1.000	0.489
	GG+GA vs. AA	Fixed	70.24	0.035	1.274	0.751-2.161	0.899	0.369	1.000	0.752
	GG vs. GA+AA	Fixed	0.00	0.472	1.120	0.758-1.655	0.568	0.570	1.000	0.530
LPER rs1137101										
Overall	G vs. A	Fixed	0.00	0.896	1.017	0.798-1.296	0.137	0.891	NA	NA
	GA vs. AA	Fixed	38.77	0.201	1.045	0.767-1.423	0.280	0.779	NA	NA
	GG vs. AA	Fixed	57.35	0.126	1.004	0.505-1.995	0.011	0.991	NA	NA
	GG+GA vs. AA	Fixed	0.00	0.388	1.062	0.788-1.432	0.396	0.692	NA	NA
	GG vs. GA+AA	Fixed	66.92	0.082	0.814	0.441-1.502	-0.660	0.509	NA	NA

NA: Not Applicable

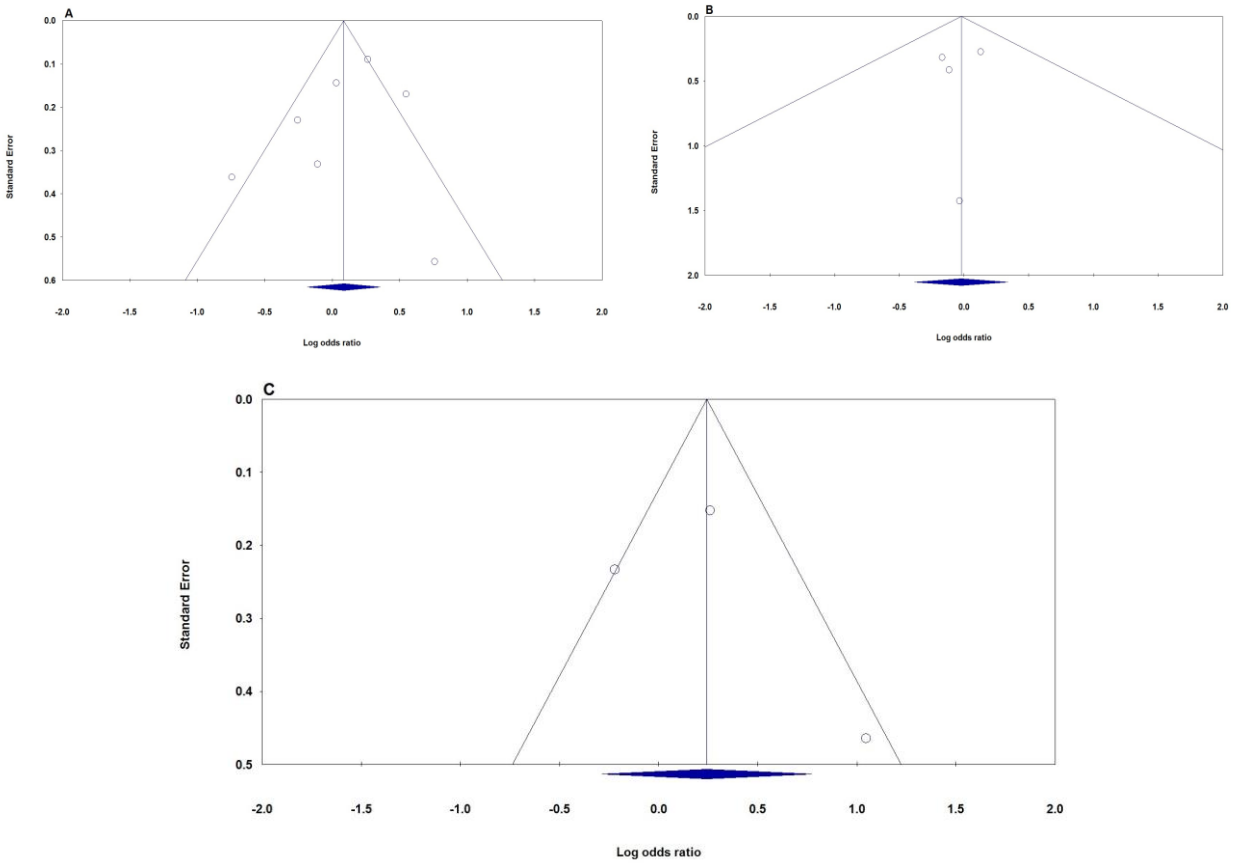

Figure 5. The funnel plots of publication bias for correlation of FTO and LEPR polymorphisms with GDM risk. A: FTO rs9939609 (allele model: A vs. T); B: FTO rs8050136 (homozygote model: AA vs. CC); and C: LPER rs1137101 (dominant model: GG+GA vs. AA).

Our combined data illustrated that the *FTO* rs9939609 and rs8050136 polymorphism were substantially correlated with GDM risk. In 2018, three meta-analyses analyzed the risk between *FTO* polymorphisms and predisposition to GDM, but their results were different. He et al., in a meta-analysis, established on seven research with 1706 GDM cases and 3574 controls announced that there was no substantial correlation between *FTO* polymorphisms (rs8050136, rs1421085, and rs9939609,) and risk of GDM.[55] Lin et al., in a meta-analysis established on seven research, illustrated that the *FTO* rs9939609 polymorphism was a potential biomarker for GDM risk prediction. Nevertheless, their results on *FTO* rs8050136 and rs1421085 polymorphisms established in three and two research illustrated that neither of them was correlated with GDM risk.[56] In another meta-analysis, Guo et al., indicated that the *FTO* rs9939609 and rs8050136 polymorphisms were substantially correlated with predisposition to GDM.[52]

LEP and LEPR are correlated with mechanisms regulating puberty onset, fertility, and pregnancy.[57] During pregnancy, as a result of elevated fat mass and mother leptin immersion escalates to 3-fold than unpregnant women, with the apex happening around 28 weeks of pregnancy.[35] As far as we know, this was the first meta-analysis on the correlation of the *LEP* rs7799039 and *LPER* rs1137101 polymorphisms with GDM risk. Our combined data demonstrated that the *LEP* rs7799039 and *LPER* rs1137101 polymorphisms were not correlated with GDM risk. Yang et al., in a study, demonstrated that a high level of plasma leptin is correlated with GDM. Nevertheless,

their findings illustrated that *LEP* rs7799039 and *LPER* rs1137101 polymorphisms were not correlated with GDM risk.[35] In another study, Anghebem-Oliveira et al. announced that the *FTO* rs1421085 and *LEPR* rs1137101 polymorphisms were not correlated with susceptibility to GDM in a Brazilian population.[42] Inconsistent with our findings, Pawlik et al., showed a correlation between *LEP* polymorphism and substantial risk of GDM in Polish pregnant women.[21]

Certain limitations of this meta-analysis must be taken into consideration. First, the number of comprised surveys to measure the correlation of *FTO*, *LEP*, and *LEPR* polymorphisms with the risk of GDM was somewhat small which can be the cause of reduced statistical power. Second, the insufficient sample size for LEP and LEPR polymorphisms may be the cause of not meaningful conclusions. Third, only studies performed among Caucasian, Asian, and Latin people were incorporated in the current meta-analysis. Thus, the inconsistency of the correlations in various ethnicities must be interpreted conservatively. Fourth, the strength of the correlations was computed via unaccustomed ORs for confounding factors such as age, antenatal age, diagnostic standards, and environmental considerations owing to a lack of baseline data, which potentially affected our achievements. Eventually, GDM is a complex disease, and interrelations between genetic and environmental factors are likely to affect the onset of this condition. In this meta-analysis, gene-gene, gene-environment interactions, and epigenetic effects were not computed because of the limited accessibility of the kind of data.

Conclusion

Considering all the results, this meta-analysis demonstrated that the *FTO* rs9939609 and rs8050136 polymorphisms were correlated with substantial risk of GDM. Nonetheless, none of the FTO rs1421085, *LEP* rs7799039, and *LPER* rs1137101 polymorphisms assessed in this meta-analysis were correlated with GDM risk. Nevertheless, larger and more rigorous studies among various ethnicities are needed in the aid to evaluate the correlation of *FTO*, *LEP*, and *LEPR* polymorphisms with GDM.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethical Considerations

This article does not contain any research with human participants or animals performed by any of the authors.

Author's Contribution

SAD, MKZ and HN: Methodology, conceptualization, investigation.
FA, RB, MN: Software, investigation, writing, original draft preparation.
JSY and HN: Investigation.
SAD, JSY, and HN: Investigation, writing.
HN, MN and SAD: Methodology, software.
SAD, RST and AT: Formal analysis, investigation.
RST and AT: Project administration
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