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Relationships of ABO and Rhesus blood groups with type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract

Objectives: The susceptibility to type 2 diabetes mellitus (T2DM) has been linked to blood type. We aimed to characterize the relationships of the ABO and Rhesus blood groups with T2DM.

Methods: Literature searches were performed using the Medline, PubMed, Scopus, Cochrane, EMBASE, and Google Scholar databases to identify studies published up to 31 March 2022. The PRISMA guidelines were used for reporting. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were obtained using fixed-effects models.

Results: Twenty-six studies of 6870 patients with T2DM and 11,879 controls were identified. Compared with the other ABO groups, people with blood type B were at higher risk of T2DM (OR: 1.30, 95% CI: 1.20–1.41), while group O was associated with a lower risk (OR: 0.92, 95% CI: 0.86–0.98). There were no significant associations of T2DM with blood types A or AB, or Rh factor.

Conclusion: Individuals with blood type B are at higher risk of developing T2DM. Therefore, they should be screened for T2DM on a frequent basis and be made aware of the importance of maintaining a balanced diet and regular exercise for the prevention of obesity and T2DM.

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Type 2 diabetes mellitus, ABO blood group, Rhesus blood group, meta-analysis, systematic review, association, heterogeneity

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Introduction

Human ABO blood group antigens manifest as various transfusion phenotypes and are glycoconjugate structures that are located on the surface of red blood cells, where they play an important role in cellular physiology and pathology.[1] Although the physiological significance of ABO antigens and the corresponding natural anti-A and anti-B isoagglutinins remains poorly understood, they are known to be important during blood transfusion and cell, tissue, and organ transplantation.[2] The presence or absence of antigens corresponding to specific blood types leads to differences in the blood that have indirect effects on susceptibility to certain infectious[3,4] and non-infectious diseases.[5] Previous studies have shown close associations between ABO blood groups and a variety of diseases, including cancer, cardiovascular disease, cognitive disorders, and metabolic disorders, such as hypertension, obesity, dyslipidemia, and diabetes mellitus.[1,6]

Diabetes mellitus is a metabolic disorder caused by defects in insulin production and/or action and is one of the most common diseases worldwide, being associated with high levels of morbidity and mortality.[7] ABO and Rh blood group phenotypes have been shown to be associated with various disorders, including type 2 diabetes mellitus (T2DM),[2] which may be underpinned by inherited differences in immunoglobulins.[8] A number of contributing factors, including genetic predisposition, and immunological and environmental factors, have significant effects on the pathogenesis and outcomes of T2DM. ABO and Rh blood groups are genetically predetermined; therefore, they may be genetically linked with other diseases with a substantial genetic components, such as DM.[9] T2DM susceptibility genes are located on the human 1q21-q23 chromosome region,[10,11] whereas the ABO blood group genes are on chromosome region 9q34.2, which commonly shows variations.[12] Better knowledge of the links between T2DM and the ABO or Rh blood groups may assist with the prevention of T2DM by facilitating the avoidance of potential predisposing factors and help clinicians identify individuals who are susceptible to this disease.

Recent studies have shown that some ABO type antigens are risk factors for T2DM, whereas others have preventive effects. In addition, Rh blood group negativity and positivity have been shown to be protective or risk factors for T2DM in different studies.[13–15] Therefore, we aimed to perform a meta-analysis of the results of previous studies to improve knowledge regarding the associations of ABO and Rh blood groups with T2DM.

Methods

Study design and reporting

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol (PRISMA-P

2020 guidelines; Supplementary Table S1).[3] As such, there was no requirement for ethics approval or informed consent for the study. The study protocol for this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42022353945.

Eligibility criteria

We included full-text articles that were published in peer-reviewed journals, and the participants in the studies described were of a range of ethnicities and socioeconomic levels. All comparative cross-sectional and case-control studies that contained clearly presented data regarding the ABO and Rh blood groups of patients with T2DM and controls that could be readily extracted. Letters to the editor, reviews, abstracts, simple cross-sectional studies, articles published in languages other than English, and those that did not report ABO and Rh blood type data for both cases and controls, or in which these data were difficult to extract, were excluded.

Information sources and search strategy

For the systematic review, relevant articles were identified by searching for publications regarding the associations of the ABO and Rh blood group antigens with T2DM in the Medline, PubMed, Science Direct, Cochrane, EMBASE, and Google Scholar databases. All the published articles regarding associations of the ABO and Rh blood types with T2DM that were published in English up to 31 March 2022 were included. The Medical Subject Heading and key words, combined using Boolean operators, were used to identify relevant studies. The search terms were "ABO blood group system/genetics" OR "ABO blood group" OR "ABO blood type" OR "Rhesus blood group" OR "Rh factor" AND "diabetes mellitus" OR "type 2 diabetes mellitus" (Supplementary Table S2). Additional studies were identified by screening the reference lists of the relevant articles and contacting appropriate authors and librarians.

Study selection and quality assessment

The retrieved articles were imported into EndNote X7 (Thomson Reuters, Toronto, Canada) to organize them and remove duplicate articles. Studies that conformed with the inclusion and exclusion criteria were selected independently by two reviewers (SG and BB), with disagreements resolved through discussion and with reference to a third reviewer (TA). The quality of reporting and the methodological quality of the included studies were assessed using the Newcastle Ottawa Scale (NOS),[17] a nine-point scale that includes points for the process of selection of the cases and controls (0–4 points), the comparability of the cases and controls (0–2 points), and the identification of the exposure and outcomes for the study participants (0–3 points). A study can be awarded maximums of 4 points for selection, 2 points for comparability, and 3 points for outcome. Quality assessment was independently performed by two authors (MA and YBW), and any disagreement was resolved by discussion. We classified studies as being of poor quality if they scored 0–3 points, fair quality if they scored 4–5 points, and good quality if they scored 6–9 points.

Outcomes of interest

The main outcomes of the study were the associations of ABO and Rh blood groups with T2DM.

Data extraction

Data were extracted by two authors after they reached a consensus regarding

conformation with the criteria listed above. The following data were extracted from the included studies: first author name, publication year, study year, country where the participants lived, sample size, and the ABO and Rh blood group distributions among cases (with T2DM) and controls.

Statistical analysis

Statistical analysis of the included studies were performed using Stata 11.0 statistical software (StataCorp, College Station, TX, USA). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify the associations of the ABO and Rh blood groups with T2DM. Heterogeneity analysis of the included studies was performed using Higgin's I^2 statistic, to determine whether fixed-effect or random-effect models should be used. A random-effects model would have been used when there was high heterogeneity ($I^2 \geq 30\%$ or $P \leq 0.05$) and a fixed-effects model was used when there was lower heterogeneity ($I^2 < 30\%$ or $P > 0.05$).[18,19] Sub-group and sensitivity analyses were not performed because of the absence of significant heterogeneity. Egger's regression test statistics and visual inspection of funnel plots for symmetry were used to evaluate publication bias.[20,21] $p < 0.05$ was regarded as indicating statistical significance.

Results

Identified studies

A total of 2149 articles were retrieved from the electronic databases and through manual searches. Of these, 818 articles were subsequently removed because they were duplicates. We also excluded 1268 articles that were not relevant on the basis of screening their titles and abstracts. A further 37 articles were excluded because they were reviews, duplicates, letters to the editor, short communications, or studies that did not report the outcomes of interest. Thus, 26 articles were included in the qualitative and quantitative analyses performed in the present study (Figure 1).

Description of the included studies

Twenty-six relevant articles that met the inclusion criteria were included in the meta-analysis. All the selected articles described case–control or comparative cross-sectional studies. These studies included a total of 6870 patients with T2DM and 11,890 controls. Eight of the studies were conducted in India,[7,12,13,22–26] three in Pakistan,[27–29] three in Iraq,[8,30,31] two in Ethiopia,[14,32] and two in Malaysia;[16,33] and the remaining eight were performed in Qatar,[34] Egypt,[35] Algeria,[36] Saudi Arabia,[37] Nigeria,[38] Turkey,[39] Iran,[40] or Morocco.[41] All of the studies included both male and female patients, except the one performed by Farshori *et al.*, which only included male patients[37] (Table 1). Almost all of the included studies were awarded scores of 6–9 points on the NOS (Supplementary Table S3).

Associations of the ABO and Rh blood groups with T2DM

The relationship between ABO blood group and T2DM was analyzed by calculating the odds of participants with T2DM having each blood group, compared with the controls, using a fixed-effect model. We found that people with blood type B were at a higher risk of T2DM than those with other types (OR: 1.30, 95% CI: 1.20–1.41) (Figure 2). The results of the heterogeneity testing for the blood group B and non-B groups were $I^2 = 13.6\%$ and $P = 0.266$. In contrast, people with blood type O were at a lower risk of T2DM than those with other types (OR: 0.92, 95% CI: 0.86–0.98). There was no significant heterogeneity between the studies with respect to participants

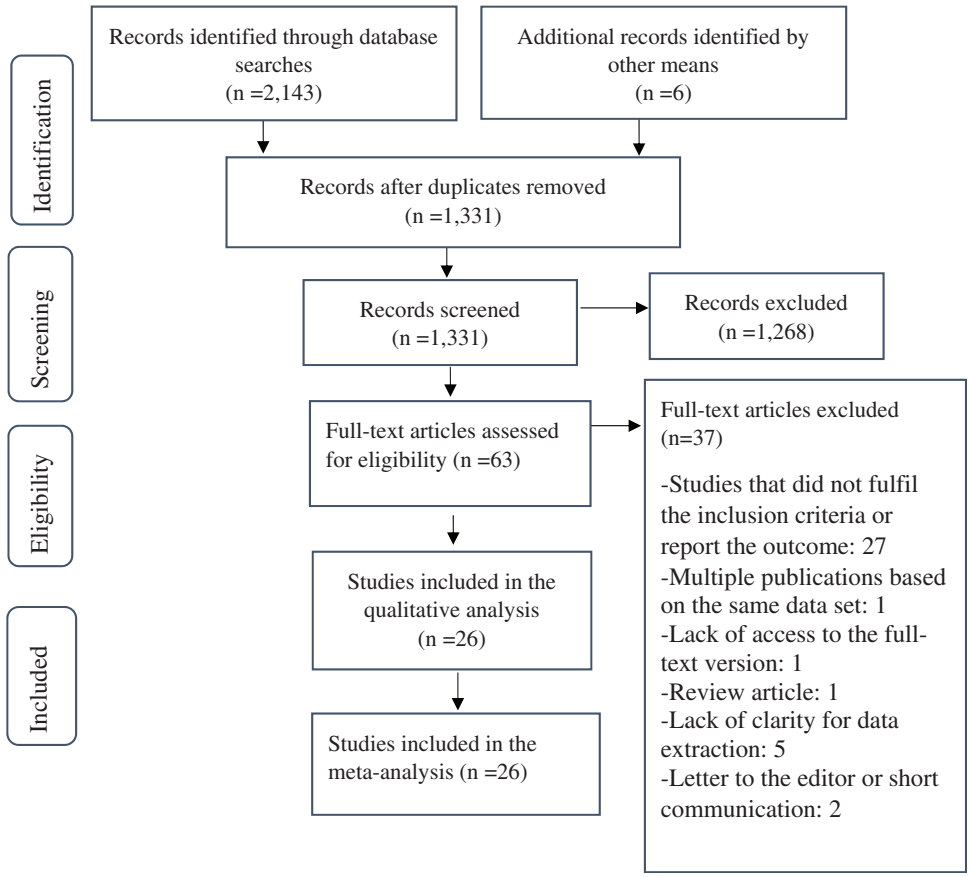

Figure 1. Flow chart describing the selection process of the included studies.

with blood group O and those with other groups ($I^2 = 0.0\%$ and $P = 0.520$) (Figure 3).

The meta-analysis showed that people with blood group A were no more likely to have T2DM than those with other blood groups (OR = 1.04, 95% CI: 0.97–1.12). There was no significant level of heterogeneity between the studies of participants with blood group A and those with other groups ($I^2 = 0.0\%$ and $P = 0.997$) (Figure 4). The results of the heterogeneity test for studies of participants with blood group AB and those with other groups were $I^2 = 0.0\%$ and $P = 0.999$, and the meta-analysis showed that having blood group AB did not affect the risk of T2DM (OR = 1.03, 95% CI: 0.92–1.16) (Figure 5). Moreover, there was no significant association between Rh blood group and T2DM (OR = 0.91, 95% CI: 0.78–1.06). The level of heterogeneity among studies of participants who were Rh-positive or Rh-negative was not significant ($I^2 = 0.0$ and $P = 0.697$) (Figure 6).

Publication bias

The included studies of the relationships of blood groups with T2DM were assessed for publication bias by the visual inspection of

Table 1. Description of the studies included in the meta-analysis of the relationships of the ABO and Rh blood groups with T2DM.

Author and year	Year of study	Country	Number of patients with T2DM	Blood group in patients						Number of controls	Blood group in controls					
				A	B	AB	O	Rh +ve	Rh −ve		A	B	AB	O	Rh +ve	Rh −ve
Waseem *et al.*, 2012[27]	2011	Pakistan	201	51	58	30	32	176	25	233	63	77	23	70	215	18
Aggarwal *et al.*, 2017[22]	2017	India	104	17	32	19	36	100	4	1,212	278	446	132	356	1,158	54
Basak *et al.*, 2016[13]	2011–2014	India	278	58	124	26	70	264	14	412	82	159	41	130	387	25
Legese *et al.*, 2020[14]	2019	Ethiopia	212	59	70	9	74	191	21	212	68	40	7	97	195	17
Tasneem *et al.*, 2021[28]	2020	Pakistan	179	48	71	40	20	68	111	50	18	7	8	17	34	16
Kamil *et al.*, 2010[33]	2009	Malaysia	70	11	25	10	24	–	–	140	35	31	19	55	–	–
Dali Sahi *et al.*, 2011[36]	2008–2009	Algeria	280	82	39	11	148	240	40	271	96	47	11	117	235	36
Navabi *et al.*, 2020[40]	2018	Iran	375	154	67	32	122	–	–	375	126	64	36	149	–	–
Sharjeel *et al.*, 2021[29]	2020–2021	Pakistan	97	21	14	57	5	–	–	97	18	14	31	34	–	–
El-Sayed *et al.*, 2015[35]	2013–2014	Egypt	160	60	50	20	30	–	–	200	65	75	20	40	–	–
Berhanie *et al.*, 2020[32]	NR	Ethiopia	120	50	30	11	29	113	7	202	61	39	16	86	184	18
Nagpal *et al.*, 2015[7]	NR	India	73	22	13	3	35	71	2	180	44	55	13	68	169	11
Kehailou *et al.*, 2019[41]	2018	Morocco	266	89	50	18	109	251	15	257	75	37	16	129	234	23
Al-Ganimi, 2018[8]	2016–2017	Iraq	150	21	29	35	65	132	18	150	36	29	30	55	137	13
Jay *et al.*, 2020[23]	NR	India	87	29	15	5	38	84	3	226	64	65	21	76	214	12
Oner *et al.*, 2015[39]	NR	Turkey	484	279	69	27	109	419	65	432	180	69	18	165	399	33
Bener *et al.*, 2014[34]	2011–2012	Qatar	1633	474	419	111	629	–	–	1,650	456	337	107	750	–	–
Okon *et al.*, 2008[38]	NR	Nigeria	224	74	26	12	118	–	–	221	54	31	17	119	–	–
Devra *et al.*, 2019[26]	NR	India	231	71	58	30	72	–	–	300	96	79	25	100	–	–
Albaroodi *et al.*, 2019[30]	2018–2019	Iraq	157	34	39	22	62	–	–	87	15	18	16	38	–	–
Dodiya *et al.*, 2016[12]	2009	India	120	29	42	13	36	–	–	630	161	224	68	207	–	–
Al-Ali *et al.*, 2008[31]	2004–2005	Iraq	259	59	76	14	110	241	18	2,480	635	659	211	975	2,268	212
Ganesan *et al.*, 2014[24]	2014	India	244	56	72	18	98	212	32	509	104	196	80	129	451	58
Mandal *et al.*, 2018[25]	2013–2014	India	276	63	113	29	71	–	–	111	22	41	9	29	–	–
Farshori *et al.*, 2016[37]	2008–2015	Saudi Arabia	342	85	104	16	137	331	11	490	116	121	26	227	438	52
Sukalingam *et al.*, 2015[16]	2013–2014	Malaysia	248	55	82	30	81	196	52	752	178	140	94	340	685	67

Abbreviations: NR: not reported; T2DM: type 2 diabetes mellitus; Rh, Rhesus factor.

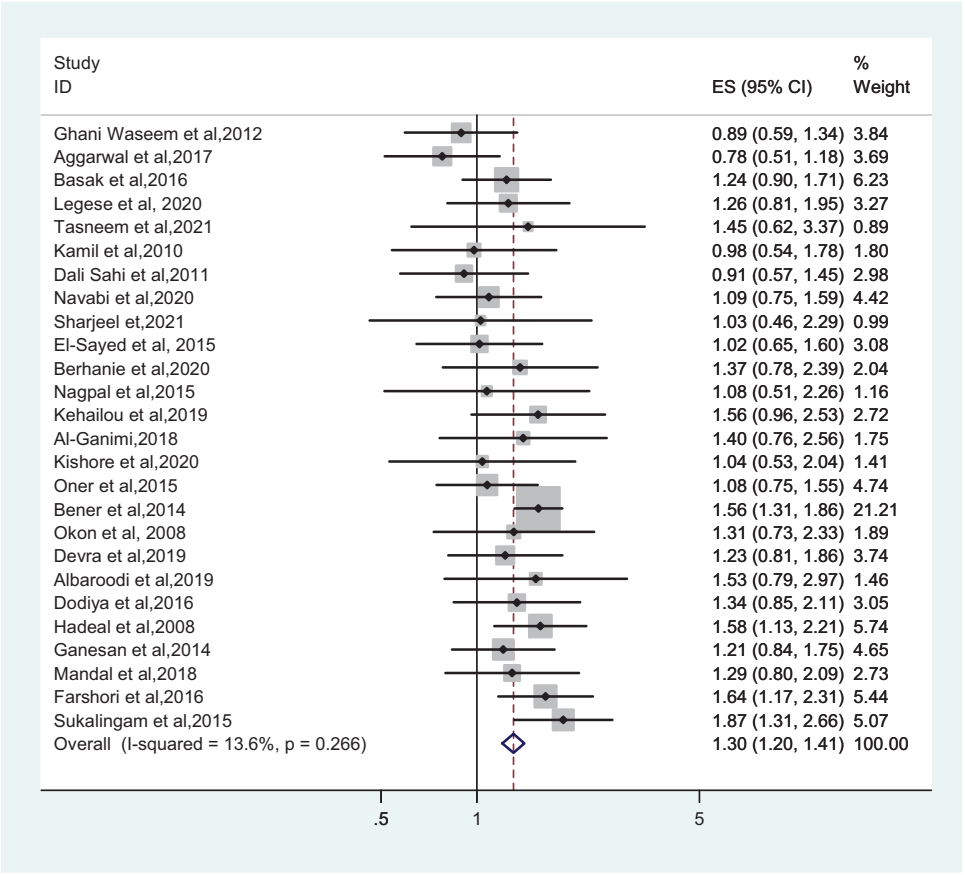

Figure 2. Forest plot of the relationship between blood group B and type 2 diabetes mellitus.

funnel plots for symmetry and Egger's test statistic. No asymmetry in the funnel plots for the relationships of the various blood types with T2DM was identified, and Egger's test showed no significant publication bias for individuals with blood group A *versus* other groups ($P = 0.284$), blood group AB *versus* other groups ($P = 0.686$), blood group O *versus* other groups ($P = 0.818$), and Rh-positive *versus* Rh-negative ($P = 0.072$). However, studies that included comparisons of participants with blood group B and other groups showed significant publication bias ($P = 0.034$) (Table 2 and Figure 7).

Discussion

Antigens of the ABO blood group are found on a variety of human cells, including vascular endothelial cells and brain cells, in addition to red blood cells.[1] Links between blood group and a wide range of diseases, including obesity,[42] preeclampsia,[43] gestational diabetes,[44] gastric cancer, and cardiovascular disorders have been identified.[1] In addition, ABO blood group-related susceptibility to various viral infections, including with hepatitis B, influenza viruses, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been shown in several studies.[45,46] However, only some of

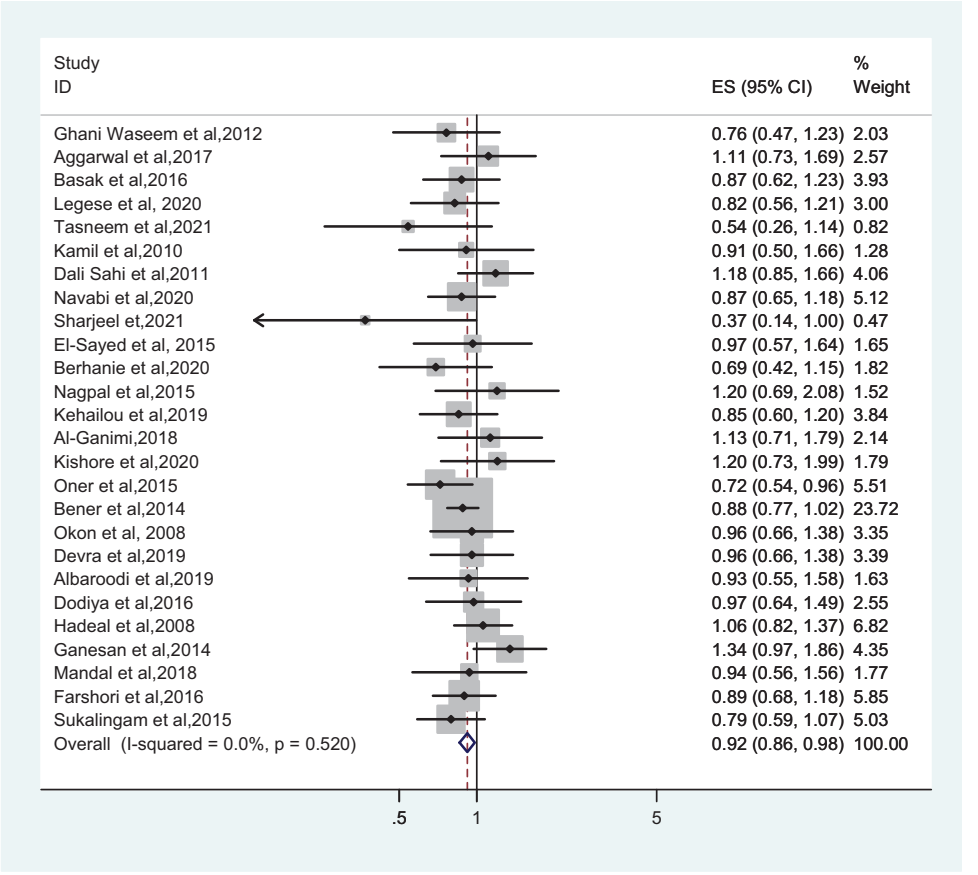

Figure 3. Forest plot of the relationship between blood group O and type 2 diabetes mellitus.

the previous studies have shown a link between T2DM and ABO blood group: some have shown no link,[15,20,47,48] whereas others have shown a positive association.[14,33] Therefore, in the present study, we explored the relationships of the ABO and Rh blood groups with T2DM by means of a systematic review and meta-analysis.

In the present study, we found that individuals with blood type B are at higher risk of developing T2DM than those with other blood types (OR: 1.30, 95%CI: 1.20–1.41). This finding is consistent with those of a previous single-center study performed by Legese *et al.*[14] and a review study performed by Meo *et al.*[49] Several studies have also shown that blood type B is associated with higher risks of a variety of disorders, including gestational diabetes,[50] gastric and pancreatic cancer[51], and malarial infection.[52] In addition, people with blood type O were found to be at lower risk of T2DM than those with other blood types (OR: 0.92, 95% CI: 0.86–0.98). Overall, the present findings were consistent with those of some previous studies of the relationship between ABO blood group and T2DM.[14,40,49,53] Several previous systematic reviews and meta-analyses have also shown that individuals with blood type O are at lower risk of infection, including with

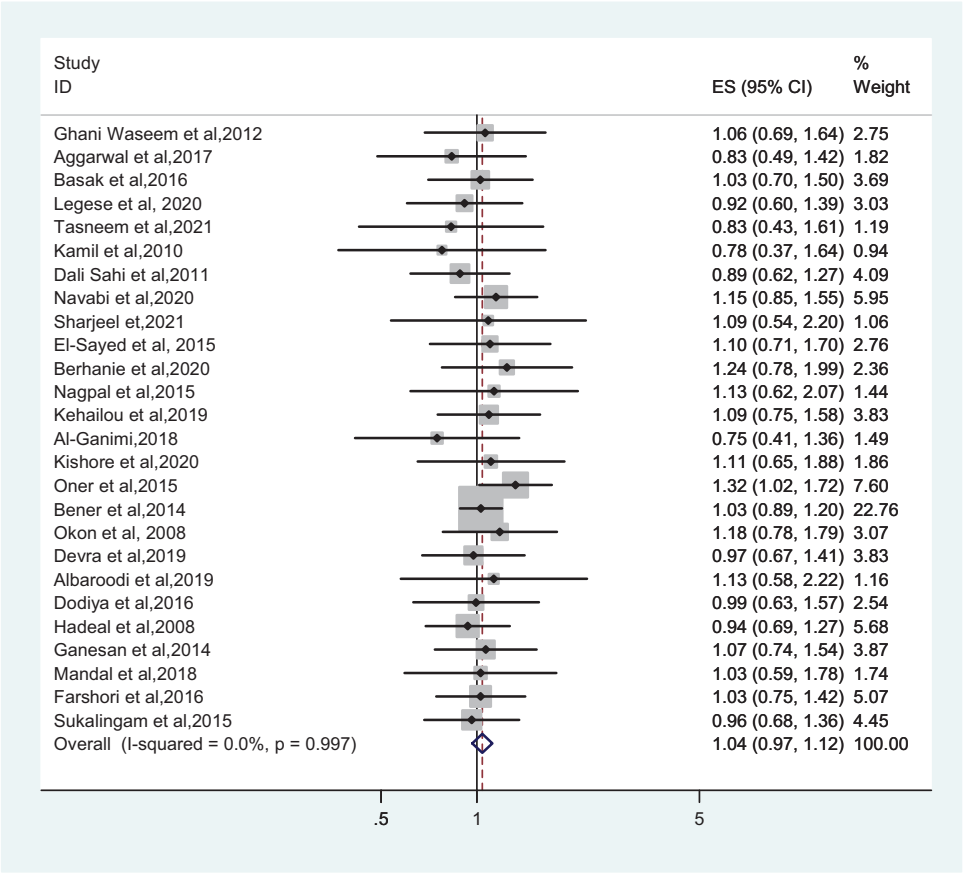

Figure 4. Forest plot of the relationship between blood group A and type 2 diabetes mellitus.

SARS-CoV-2,[45,54] and preeclampsia.[43] In contrast, other studies have shown that individuals with blood type O are more likely to develop T2DM[22] and gestational diabetes,[44] *Plasmodium falciparum* infection,[55] and tuberculosis infection.[56,57]

The mechanisms underlying the observed associations have been suggested to involve endothelial and pro-inflammatory molecules, and the factor VIII–von Willebrand factor complex, plasma soluble intercellular adhesion molecule 1 (ICAM-1), and tumor necrosis factor receptor 2 (TNF-R2) concentrations are higher in individuals with blood groups other than O.[58,59] Insulin resistance is associated with systemic inflammation, and both contribute to the development of T2DM.[60] In addition, the ABO blood group is a genetically determined host factor that influences the composition of the gut microbiota, which has also been shown to affect glucose metabolism, energy balance, and the level of inflammation present.[61]

No associations were found of the blood groups A and AB with T2DM (OR = 1.04, 95% CI: 0.97–1.12 and OR = 1.03, 95% CI: 0.92–1.16, respectively) in the present study, consistent with the findings of previous studies performed in western Algeria,[36] India,[62] and Bangladesh,[15] which also showed no associations between the ABO

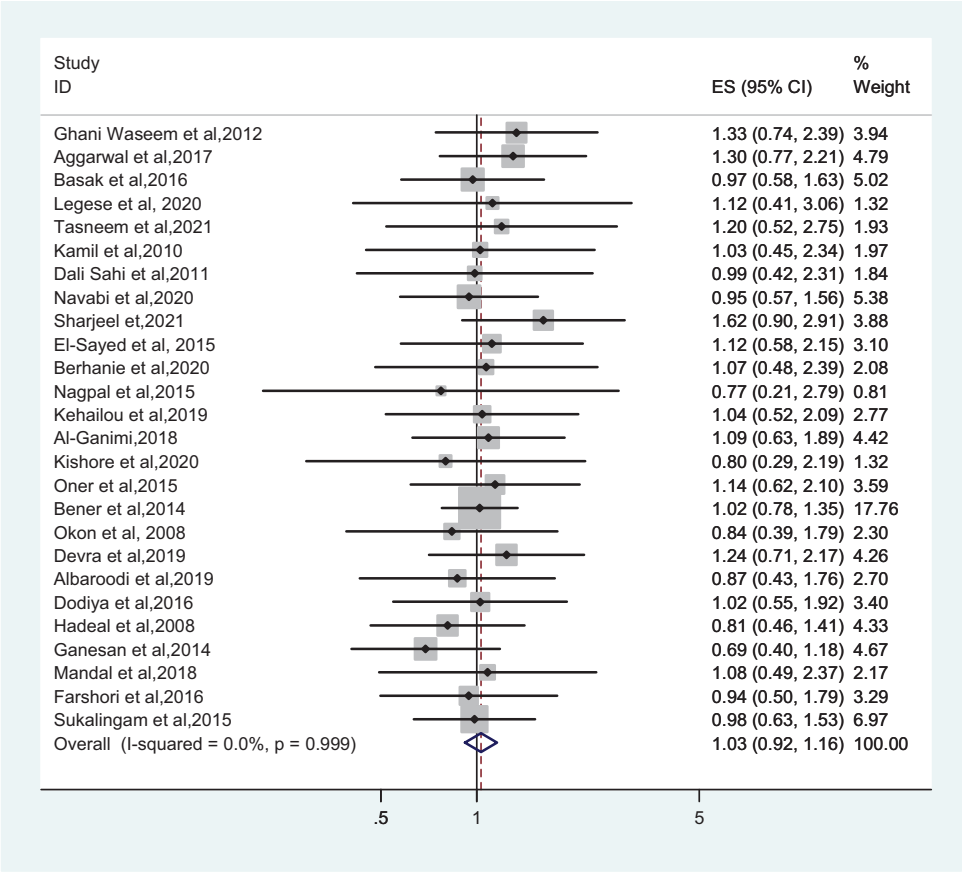

Figure 5. Forest plot of the relationship between blood group AB and type 2 diabetes mellitus.

blood groups and T2DM. In contrast, previous studies have shown that individuals with blood group A are more likely to develop T2DM[38,40] and to have higher insulin and random blood glucose concentrations.[35] In addition, a study by Salem *et al.* performed in Egypt showed that blood type A is more common in patients with rheumatic disease.[4]

We also found no significant association between Rh blood group and T2DM (OR = 0.91, 95% CI: 0.78–1.06), as previously shown in studies conducted in India,[22] Algeria,[36] and Ethiopia.[14] However, a study by Stern *et al.* showed a statistically significant association between T2DM and Rh blood type.[63] Similarly, a study performed in Iran[31] showed that Rh-positivity is positively associated with T2DM. In addition, the study by Salem *et al.* showed that Rh-positivity is more common in patients with rheumatic disease.[4] In contrast, a study conducted in Pakistan[27] showed that Rh-negativity is significantly associated with T2DM. A possible explanation for this is that the Rh blood system may be linked to glucose metabolism, and thereby affect the clinical manifestation of diabetes. Further research is necessary to better understand how specific genes contribute to the regulation of blood glucose concentration and affect susceptibility to T2DM.

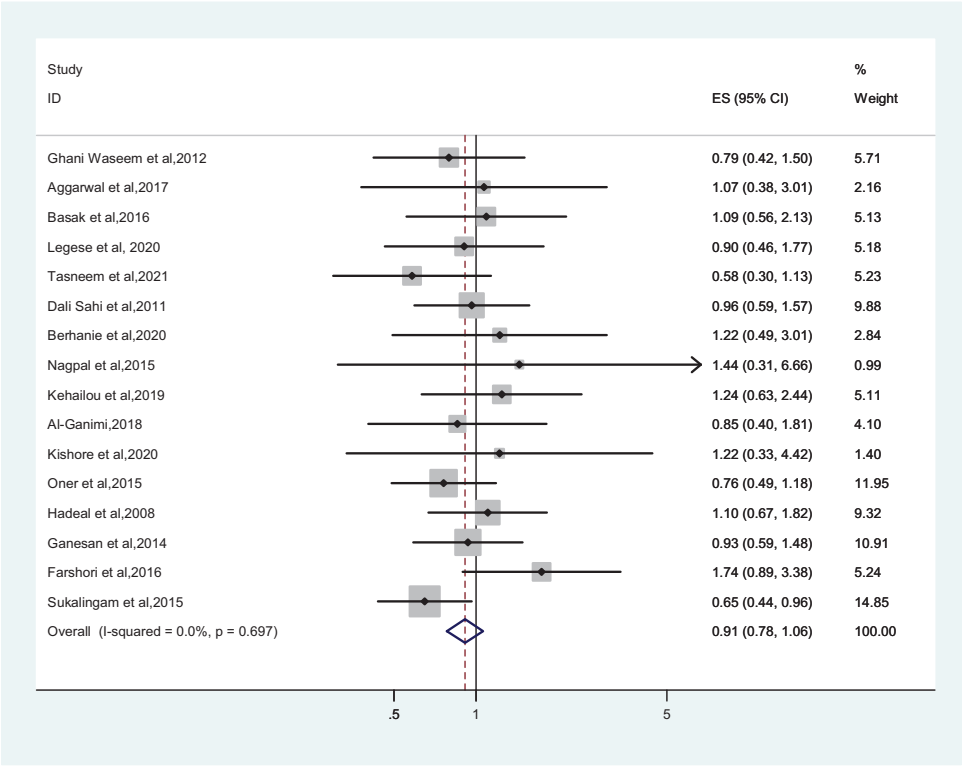

Figure 6. Forest plot of the relationship between the Rh blood group and type 2 diabetes mellitus.

Table 2. Results of Egger's tests.

Blood group	Standard error of the effect size	Coefficient	Standard error	t	P > t	95% Confidence interval
A *vs.* non-A	Slope	0.09	0.06	1.67	0.11	−0.03, 0.23
	Bias	−0.35	0.32	−1.10	0.28	−1.00, 0.30
B *vs.* non-B	Slope	0.50	0.11	4.45	<0.001	0.27, 0.73
	Bias	−1.22	0.54	−2.25	0.04	−2.34, −0.10
AB *vs.* non-AB	Slope	0.05	0.11	0.44	0.67	−0.18, 0.28
	Bias	−0.06	0.37	−0.17	0.87	−0.83, 0.70
O *vs.* non-O	Slope	−0.07	0.09	−0.76	0.45	−0.25, 0.11
	Bias	−0.12	0.49	−0.23	0.81	−1.13, 0.90
Rh-positive *vs.* Rh-negative	Slope	−0.46	0.19	−2.32	0.04	−0.89, −0.03
	Bias	1.2	0.64	1.94	0.07	−0.13, 2.62

Rh, Rhesus factor.

The clinical implications of the present findings are that individuals with blood group B are at higher risk of developing T2DM, while those with blood group O are at lower risk. This suggests that individuals with blood group B might be predisposed toward obesity and diabetes mellitus.[16] Thus, numerous factors,

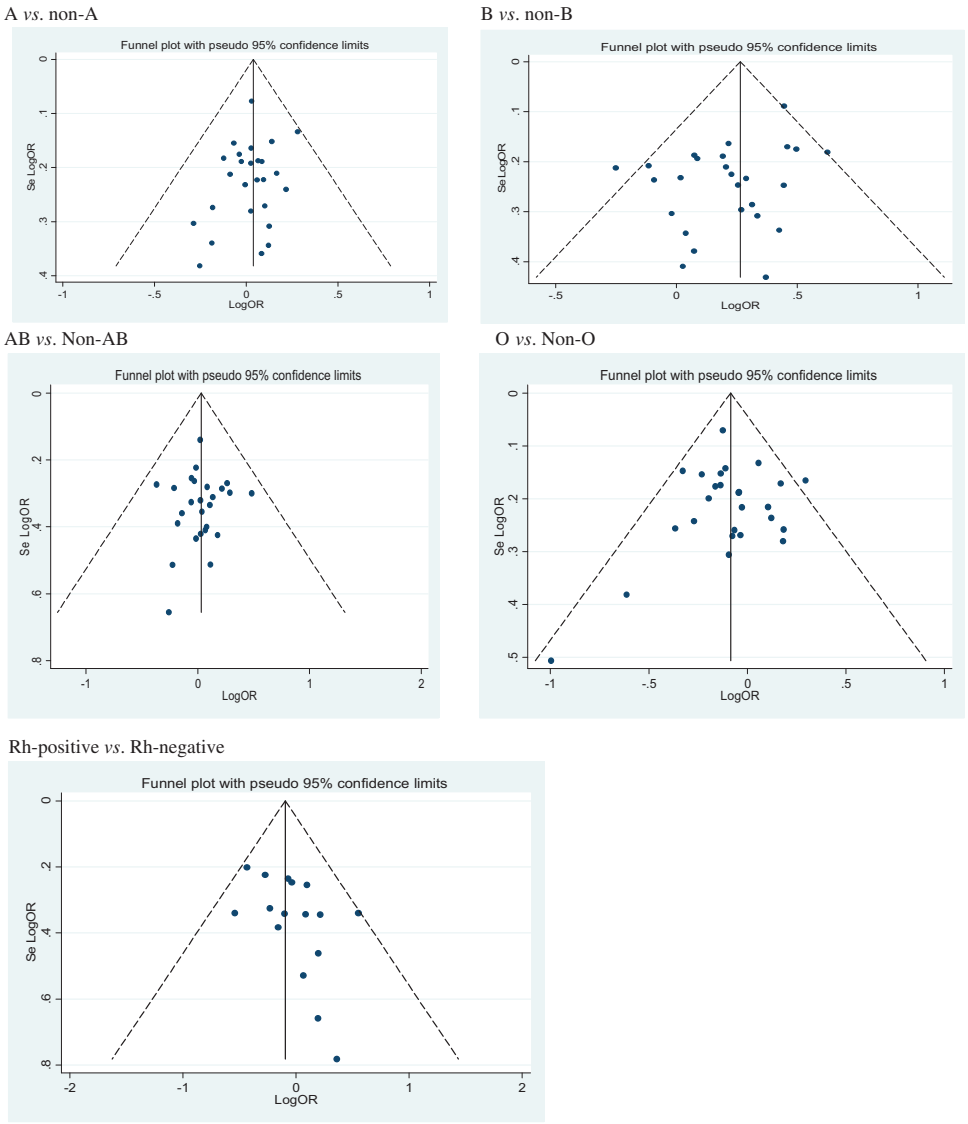

Figure 7. Funnel plot of the included studies assessing the relationships of the ABO and Rh blood groups with type 2 diabetes mellitus.

including genetic, environmental, and dietary factors, obesity, and a lack of exercise are associated with the development of diabetes mellitus.[37]

The present study has both strengths and limitations. The strengths of the study include the identification of relevant articles through a comprehensive data search that permitted the analysis of the relationships between blood groups and T2DM. In addition, the level of heterogeneity of the included studies was low, which implies that the present findings should be accurate. However, the inclusion of articles published only in English may have affected the outcomes. In addition, the use of the ABO

blood group to predict the development of T2DM is clearly inadequate on its own, but other relevant risk factors were not considered in the present study. Furthermore, the effect of differences in the distributions of the ABO phenotypes between countries was not considered in the analysis. Finally, the biological mechanism through which the ABO blood group system may influence the prevalence of T2DM has not been elucidated.

Conclusion

The findings of the present study imply that there is a link between T2DM and the ABO blood group system. We have shown that blood type B is linked to a higher risk of T2DM, whereas blood type O is associated with a significantly lower risk. However, we found no connection between the Rh blood group and T2DM. Therefore, individuals with a high risk profile should be screened for T2DM on a frequent basis and should be aware of the importance of a well-balanced diet and regular exercise for the prevention of obesity and T2DM.

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Author contributions

All the authors contributed to the literature search, manuscript drafting, statistical analysis, and quality assessment. The authors all participated in the revision of the paper, gave their approval for its submission, and agree to be accountable for all aspects of the work.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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