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Prevalence of latent autoimmune diabetes in adults and insulin resistance: a systematic review and meta-analysis

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Abstract

Latent autoimmune diabetes in adults is a form of diabetes that progresses slowly and is controlled by diet and oral glucose-lowering medications before insulin is required. The aim of the present study was to evaluate the prevalence of latent autoimmune diabetes in adults. The present study was conducted based on PRISMA 2020-27-item checklist. To find the studies conducted in line with the purpose of the study, PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases and Google Scholar search engine were reviewed from 2013 to August 2023. Meta-analysis was performed using effect size with 95% confidence interval. Data analysis was done using STATA/MP. v17 software. The present study was carried out based on the PRISMA 2020 27-point checklist. To find out which studies were carried out in accordance with the purpose of the study, from 2013 to August, the databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase and the search engine Google Scholar reviewed 2023. Meta-analysis was performed using effect size with 95% confidence interval. Data analysis was carried out using STATA/MP. v17 software. The overall prevalence of Latent autoimmune diabetes of adults was found to be 7% (95%CI 0–20). Subgroup analysis of Latent autoimmune diabetes of adults in the context of geographic regions showed a higher prevalence in North America (15%) and South East Asia (12%). Since the identification of Latent autoimmune diabetes of adult patients with other forms of diabetes is misdiagnosed due to the combination of phenotypic features with T1D and T2D, studying its prevalence is of great importance.

Key Words: latent autoimmune diabetes in adults, prevalence, type 2 diabetes, type 1 diabetes.

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According to the International Diabetes Federation's 2019 forecast, By 2035, there will be 578 million people worldwide who have diabetes, and this trend will reach 700 million people by 2045.[1] Type 1 diabetes is a type of autoimmune disease in which disorders of insulin secretion occur due to the autoimmune destruction of insulin-secreting cells.[2] Many patients with type 1 diabetes have anti-islet autoantibodies in their peripheral blood.[3] A number of diabetic who, in contrast to classic type 1, appear in adulthood and initially do not require insulin the so-called, Latent Autoimmune Diabetes of Adults (LADA), have diabetes-related autoantibodies in their blood serum.[4] The difference in autoimmunity compared to islet cells, the regulation of immune response and the response of β-cells to immune invasion may explain the wide spectrum of clinical manifestations of type 1 diabetes,[5] this ranges from acute symptoms in children to the absence of insulin dependence at the time of LADA diagnosis.[4] In most cases, patients with LADA are diagnosed as type 2 by some doctors.[6] However, these patients become dependent on insulin earlier than people with type 2 diabetes. If there is no proper control of sugar and the onset of symptoms is caused by lack of adequate treatment, there will be huge costs to the patient and the country's healthcare system.[7] The diagnostic criteria recommended by the Society of Diabetes Immunology (2005) for LADA are, 1. Age of onset in adulthood (<30); 2. Have autoantibodies related to diabetes; 3. Insulin independence should be maintained for at least 6 months from the time of diagnosis.[8] According to epidemiological reports, approximately 5 to 10 percent of all diabetes cases are related to LADA.[9] Studies have shown that the incidence of LADA varies significantly in different regions. So, the prevalence rate is much higher in some areas and lower in others. Its cause is influenced by genetic and environmental factors.[10-12]

In Asian regions, the prevalence of LADA has been less

studied compared to Europe and America; According to studies conducted in Asia, the prevalence of LADA in Asia is as high as 10%.[13-17] Considering that the prevalence rate is the same as that of type 1 diabetes and the importance of diagnosing LADA is important, the purpose of this study was to investigate the overall prevalence of LADA for clinical understanding, as well as the importance of diagnosis, treatment and examination to determine insulin resistance.

Materials and Methods

Search strategy and information sources

To find related studies, after setting the search keywords, use both MeSH keywords and search in PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI databases, Elsevier, Embase databases and the Google Scholar search engine were searched. In addition to the above databases, the sources list of selected studies as manually searched. All articles from 2013 were reviewed by the end of August 2023.

To access the articles, MeSH keywords ((“Latent Autoimmune Diabetes in Adults”[Mesh]) OR (“Latent Autoimmune Diabetes in Adults/epidemiology”[Mesh] OR “Latent Autoimmune Diabetes in Adults/etiology”[Mesh] OR “Latent Autoimmune Diabetes in Adults/genetics”[Mesh] OR “Latent Autoimmune Diabetes in Adults/mortality”[Mesh])) OR “Diabetes Mellitus, Type 2”[Mesh]) OR “Diabetes Mellitus, Type 1”[Mesh]) AND (“Prevalence”[Mesh] OR “Epidemiology”[Mesh] OR “epidemiology” [Subheading]) or all possible combinations of these words were used.

Study selection criteria

The main criteria for inclusion of articles in the current study are studies published in English that have investigated the prevalence of LADA data in diabetics patients; original research articles; patients diagnosed by fasting blood glucose or oral glucose tolerance test were included in the study. Exclusion criteria are: low quality articles; reprinted articles that used information from the same sample; Review articles, letters to the editor, or article suggestions that do not meet the criteria for definition and testing according to WHO indicators.

Selection and data collection process

Based on the search strategy and keywords, a list of all articles in the mentioned databases was first created. The articles and documents obtained from the multi-step search of title, abstract and all screening text and final studies that met the inclusion criteria were included in the statistical community. Then, selected studies were then checked for quality by two independent reviewers. In addition, if there were disagreements between the experts at each stage of selection and evaluation, a third person was consulted and a joint discussion was held. After the final selection of studies, the required information includes: first author, year of publication of the article, age group of patients, diagnostic criteria, type of study population (diabetic or normal population or clinic and hospital), total sample size, family history using a table extraction table prepared in an Excel software environment was created, was extracted and summarized. Additionally, Endnote X8 resource management software was used to organize, study, and identify duplicate titles and abstracts.

Study risk of bias assessment

The quality assessment of prevalence studies was conducted based on the design of Hoy *et al.*[18] Each study was assessed using a score of 1 (yes) or 0 (no) for a set of 9 questions, and the overall risk of an individual study was calculated by summing the scores. Studies were classified as low, medium, or high risk of bias if the score was 0-3, 4-6, or 9-7, respectively.

Data analysis

Meta-analysis was performed using effect size with 95% confidence interval. To estimate the heterogeneity of the studies, the index I^2 (<25%: weak heterogeneity, 25-75%: moderate heterogeneity, and over 75%: high heterogeneity) was used. The results were combined using the fixed effect model (Inverse–variance method) in the meta-analysis. Publication bias was checked using Egger test and Beggs funnel plot and data analysis was carried out using STATA/MP. v17 software. A p-value less than 0.05 was considered significant.

Result

The source search identified 358 articles. 71 articles were excluded from the study due to duplicates and 203 articles were excluded from the study after reviewing the title and abstracts of the articles. After reviewing the full text of 61 articles, 49 articles were excluded from the study and finally 12 articles were included in the meta-analysis. The diagram for the articles identified and included in the study is shown in Figure 1.

Study characteristics

By reviewing 12 selected articles, 25,892 patients were studied, of which 1,218 were estimated to have LADA. The characteristics of the selected studies are summarized in Table 1. The age range of diabetics was 30 to 73 years, and in all studies, LADA patients were screened and identified according to WHO diagnostic criteria. 456 people had a family history of diabetes.

Bias assessment

According to the checklist, the studies were classified as having a low to medium risk of bias; However, some studies had high and unclear bias when examining the elements examined. The mean value of the checklist across all studies was 3/9 criteria.

Prevalence of LADA

The Prevalence of LADA was 7% (ES: 7% 95%CI; 0% to 20%) with low heterogeneity (I^2=0%; P=1.00) (Figure 2). According to a sub-group meta-analysis, the prevalence of LADA was 15% in North America, 5% in the Middle East,

12% in South east Asia, 5% in Africa and 1% in Europe with no significant differences between them the groups (test of group differences: P=0.99) with low heterogeneity (I^2=0%; P=1.00) (Figure 3).

Discussion

According to the present meta-analysis, the prevalence of LADA in diabetic aged 30 to 73 years is 7%. The prevalence of LADA varied in different populations, and the highest prevalence of LADA was observed in North America and Southeast Asia. In the present study, the prevalence of LADA cases was estimated to be 0 to 20%; In studies of this prevalence in patients with type 2 phenotype, it varies between 6 and 50% in different populations.[29] One of the differences in the results may be the method of patient selection and entry and exit criteria, which has led to different results and makes the diagnosis of LADA patients difficult. The different results may also be due to methodological differences in the studies. Based on the study results of the report on the prevalence of LADA in different populations, it may be due to genetic disorders, diagnostic criteria, antibody measurement methods and characteristics of patients, and dietary habits.[30-32] The impact of family history of diabetes on LADA is not yet well known. The genetic characteristics of LADA people include the frequency of some HLA alleles, such as HLA-DQBI, as in people with type 1 diabetes.[33]

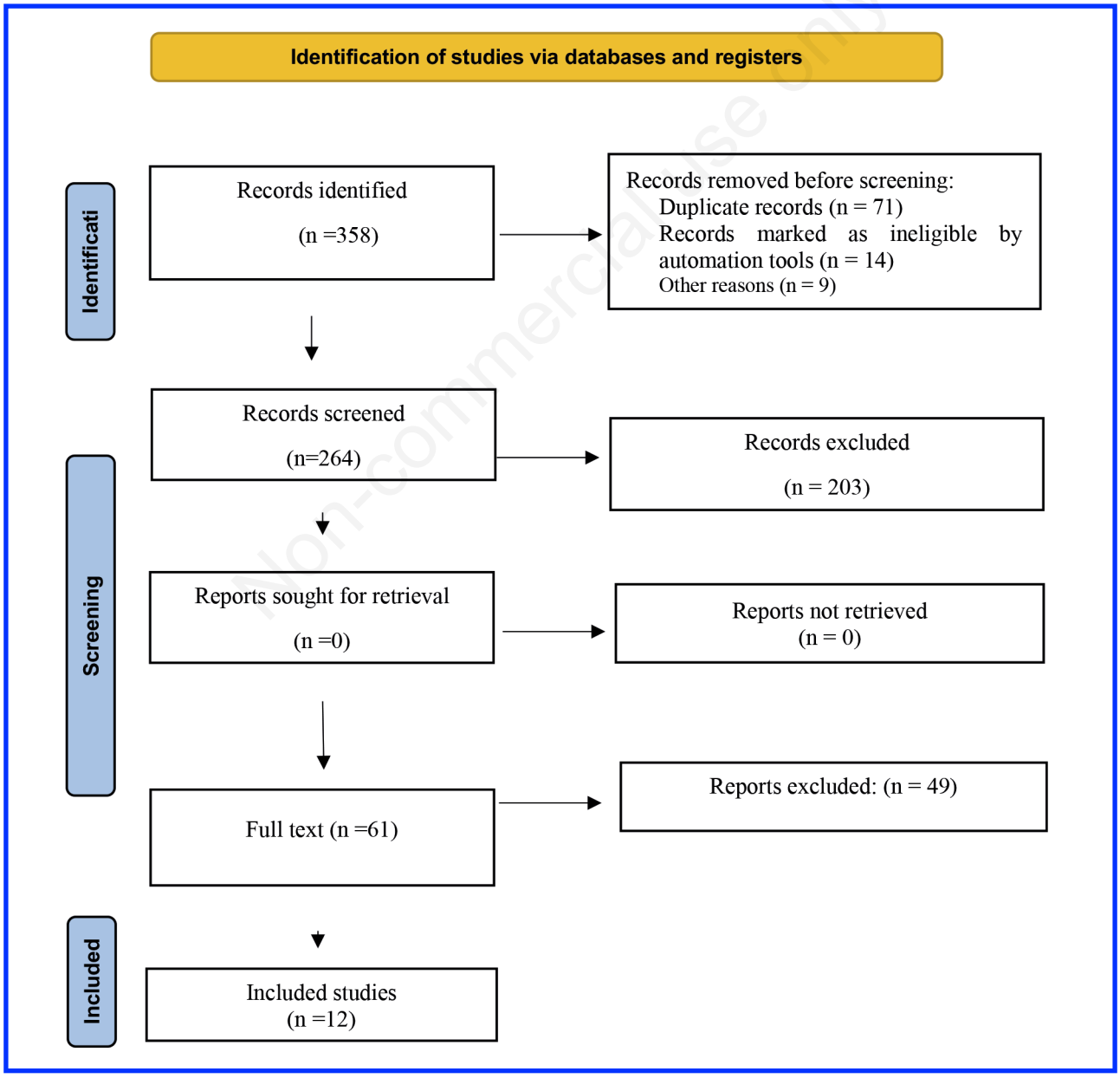

Figure 1. PRISMA 2020 Checklist.

Table 1. *Summary characteristics of studies.*

Study, years	Sample size	Number of LADA	Sex		Family historyof diabetes		Diagnostic criteria	Range of age (years)
			Male	Female	Yes	No		
Nolasco-Rosales *et al.*, 2023 [19]	377	59	NR	NR	NR	NR	NR	30-70
Manisha *et al.*, 2022 [11]	186	8	2	6	3	5	NR	30-70
Al-Zubairi *et al.*, 2021 [20]	270	12	7	5	7	5	NR	30-70
Tam *et al.*, 2020 [10]	324	5	5	0	3	2	NR	>30
Gao *et al.*, 2019 [21]	495	141	NR	NR	41	100	NR	NR
Ghanem *et al.*, 2019 [22]	1515	194	NR	NR	NR	NR	NR	35-70
Kumar *et al.*, 2017 [23]	139	9	5	4	4	5	NR	30-70
AL-Hasnawi *et al.*, 2015 [24]	280	34	14	20	21	13	NR	30-73
Maddaloni *et al.*, 2015 [25]	17072	437	212	225	310	127	NR	>30
Zhou *et al.*, 2013 [26]	4880	287	178	109	67	220	WHO	>30
Roh *et al.*, 2013 [27]	323	17	NR	NR	NR	NR	NR	
Chandni *et al.*, 2013 [28]	31	15	NR	NR	NR	NR	>30	

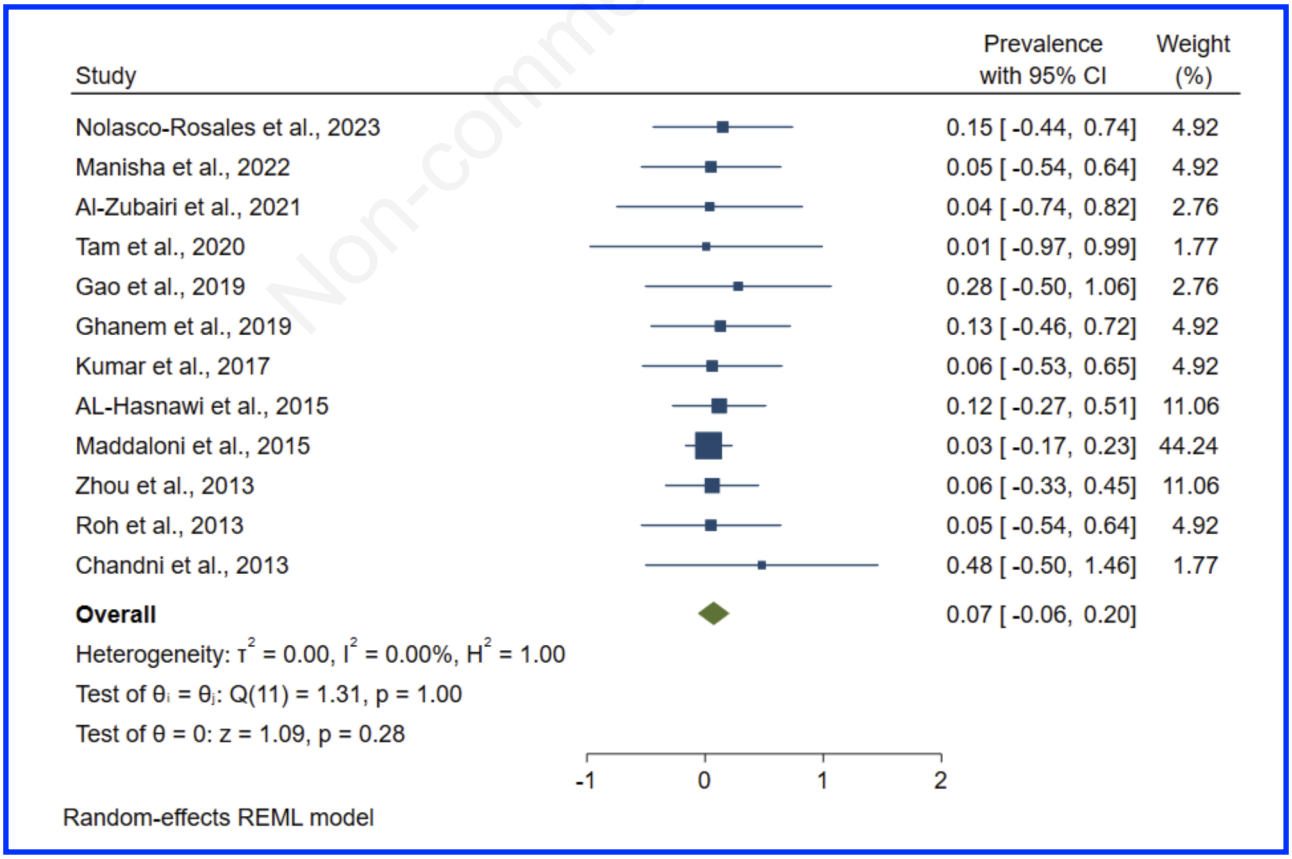

Figure 2. *Forest plot showed prevalence of LADA.*

On the other hand, the results of one study showed that 23% of LADA individuals have a family history of type 2 diabetes.[33] The results of the studies showed that 75% of people with LADA and 67% of people with type 2 diabetes have a family history of diabetes.[20,33] According to the findings of the studies, the familial type of diabetes exerts its

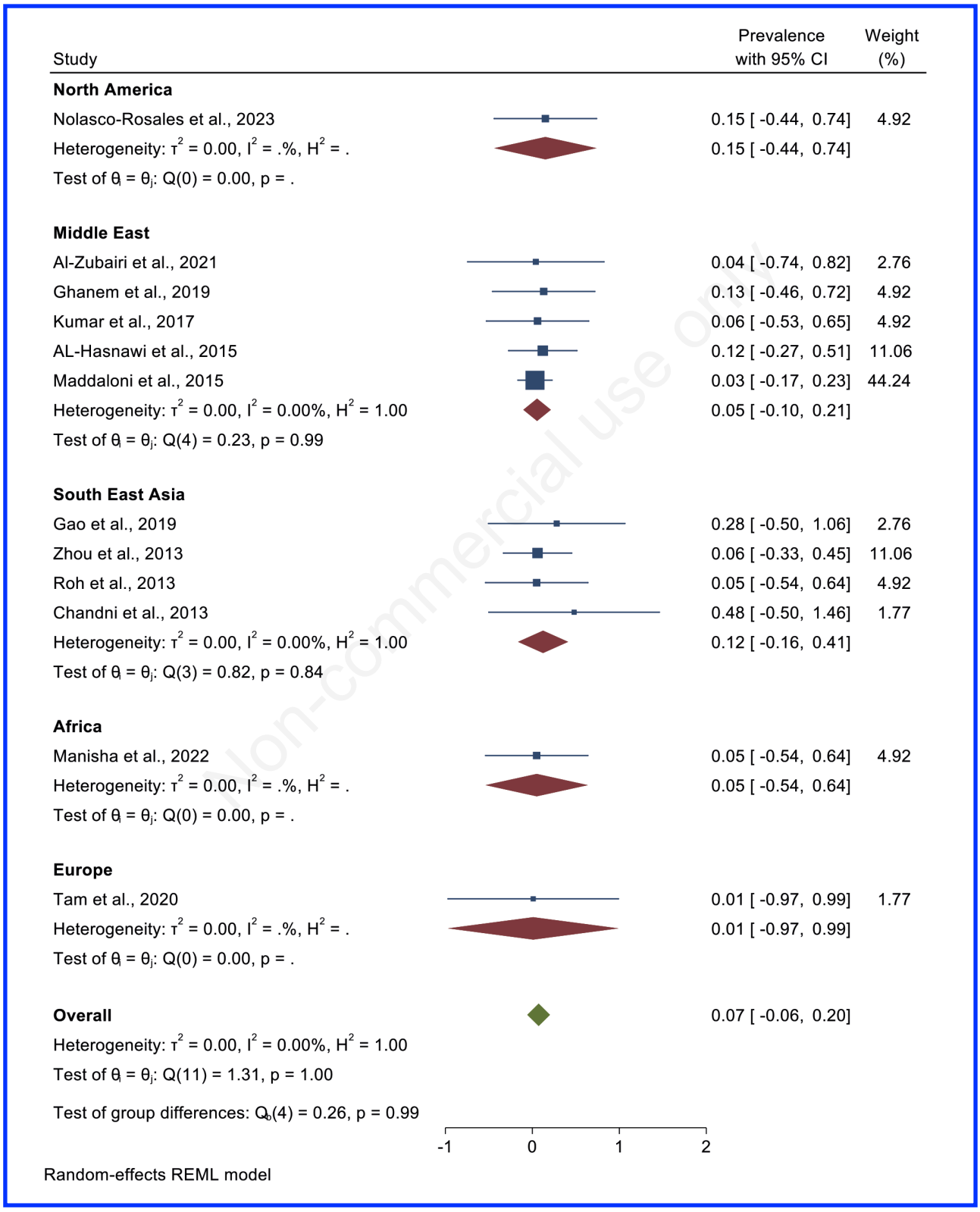

Figure 3. *Forest plot showed subgroup meta-analysis by continent.*

effect by reducing insulin, and this feature of type 2 diabetes is one of the common features with LADA. It seems that more studies with an appropriate and large sample size should be conducted to investigate the role of family history of diabetes in the occurrence of LADA and compare it with type 2 diabetes. One of the characteristics of LADA people is the initial response to oral medications, and insulin dependence occurs gradually and after some time. According to the results of the studies, most people with LADA use oral medications to control blood glucose, but the amount of C-peptide, which indicates the function of beta cells, shows that this is reduced in the LADA group compared to type 2 diabetes and the difference is statistically significant.[20] Despite the low prevalence of LADA, the lack of an accurate diagnosis and early onset of LADA can become a serious problem for the individual and his family and impose high costs on society. Therefore, it is recommended to examine people aged 30 and over.

Conclusions

In the current study, the prevalence of LADA was found to be 7%, which varies in different populations; since the identification of LADA patients with other forms of diabetes is misdiagnosed with T1D and T2D due to the combination of phenotypic features, studying their prevalence is of great importance; identification of this group of patients is necessary to develop an appropriate treatment approach that delays the autoimmune process and the destruction of the remaining beta cells.

List of acronyms

LADA: Latent autoimmune diabetes in adults.
T1D: Type 1 diabetes.
T2D: Type 2 diabetes.
WHO: World Health Organization.

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval

Not applicable.

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