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Global Clinico-epidemiologic Pattern of Childhood Vitiligo: A Systematic Review and Meta-Analysis

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Running head:

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Abstract

Background: Childhood vitiligo is different from adult vitiligo in many aspects. There is no systematic review of different aspects of clinico-epidemiologic patterns of vitiligo in children. This study aimed to review the characteristics of vitiligo among the pediatric population.

Methods: A systematic search was done with MeSh-based keywords on online databases including PubMed, Scopus, and Web of Sciences. The records were evaluated and the eligible articles were selected. The selection of articles was done through three steps. The clinico-epidemiological data were then extracted and imported to STATA software for meta-analysis.

Results: The meta-analysis of 17 studies, including 4365 subjects demonstrated there were 2475 females (Estimated = 56.8%, 95% CI 54.45 - 59.22). Female to male ratio of 1.3:1 was identified. Meta-regression showed a significant association between continents and gender (P=0.03). The most common types of non-segmental vitiligo were vulgaris (42.49%), focal (27.21%), and acrofacial (17.8%). Pooled non-segmental to segmental ratio was 4.6:1. The lowest and highest ratios were noted in America with two studies (Estimated = 3.02, 95% CI 1.54 – 4.50) and Africa

with one study (Estimated = 11.56, 95% CI -0.98 – 24.10), respectively. Using meta-regression, the association between continents and vitiligo type was insignificant (P=0.47). Positive family history was recorded in 657 patients (Estimated = 16.88%, 95% CI 13.37– 20.39). Concerning the country of study, positive family history ranged from 13.91% (Asia with 11 studies) to 27.01% (Europe with 2 studies) (P=0.11). Kobner phenomena and leukotrichia were noted in 687 (25.47%) and 461 (18.52%) patients, respectively.

Conclusion: The review revealed that childhood vitiligo is more common in females. The most common types of childhood vitiligo were non-segmental including vulgaris, focal, and acrofacial. Clinico-epidemiologic pattern of childhood vitiligo is variable in different geographic areas.

Keywords: Childhood; Depigmentation; Epidemiology; Pediatric; Systematic Review; Vitiligo

Key messages

What is already known on this topic: Vitiligo is a life-altering condition. Childhood vitiligo is different from adult vitiligo in many aspects.

What this study adds: Currently, there is no clear picture of the clinico-epidemiologic pattern of childhood vitiligo in the world, and this review details these characteristics of vitiligo in children.

How this study might affect research, practice, or policy: Awareness of the typical pattern of childhood vitiligo in different geographic areas and its related factors in the world provides a better understanding of clinical disease identification and management.

Introduction

Vitiligo, as an acquired autoimmune inflammatory disease of the skin, is a life-altering condition. The disease is mainly associated with significant cosmetic concerns and significant psychological effects including the social stigma that affect the self-esteem of affected individuals (1).

Childhood vitiligo is different from adult vitiligo in many aspects (2). Negative experiences from childhood vitiligo may influence adult life (3). Recent studies in the United States showed 1.9 million cases have been diagnosed with vitiligo and its prevalence is 0.76 % (4). However, in other countries, its prevalence is different from 0.5 % to 2 % (5). The exact prevalence of vitiligo in children is unknown but approximately at least about 25% of vitiligo cases begin before the age of 10 years (6). Although very early onset vitiligo is also reported, the existence of true 'congenital vitiligo' remains controversial (7).

The exact mechanism of vitiligo is not completely understood. The autoimmune mechanism, neurogenic mechanism, and self-destructive mechanism are among mentioned theories (8). Exposure to environmental triggers such as trauma and sun exposure have also a significant role in vitiligo pathogenesis (9). Some studies also reported its association with other autoimmune diseases including hypothyroidism, diabetes mellitus, alopecia, anemia, lupus, rheumatoid arthritis, and psoriasis. Also, this disease is more prevalent among people with a positive family history of vitiligo (10).

Childhood vitiligo is different from adult vitiligo for several characteristics including a high prevalence of segmental variant, a higher prevalence of halo nevi, and a more prevalent family history of autoimmune diseases. Childhood vitiligo can affect all races but the prevalence and pattern of the disease probably vary according to geographic origin.

Understanding the clinico-epidemiologic characteristics of vitiligo among the pediatric population seems to correlate with good treatment outcomes (7). Some epidemiological studies described the clinico-epidemiologic characteristics of vitiligo in pediatrics. However, there is not any comprehensive review in this regard. This study aimed to review the characteristics of vitiligo among the pediatric population through a systematic review and meta-analysis.

Methods

Literature search strategy

This is a systematic review and meta-analysis for the evaluation of the clinico-epidemiologic features of vitiligo in children. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was considered for performing this systematic review. After consultation with experts in the field of dermatology and pediatrics dermatology, appropriate keywords were selected based on the MeSh databases. The search was done on 2022 June. PubMed, Scopus, and Web of Sciences were searched. All databases were searched by the below queries limited to the title: ((vitiligo) AND (epidemiology OR Clinical OR characteristics)) AND (Child OR Pediatric OR Children OR Infants OR Neonate)). Also, a non-systematic search was done in an explorer manner in Google to find any missed articles and gray literature.

Inclusion and Exclusion Criteria

Studies were eligible if they met all of the following inclusion criteria: (a) they were observational epidemiological studies; (b) they included patients with vitiligo with the age of under 18 years. Conference articles, abstracts, protocols, Narrative and systematic reviews, and consensus opinions; and also, articles that were published in non-English languages were excluded from the study. No time limitation also was considered.

The records were imported into EndNote X8 software (V8.0.1. Clarivate Analytics). The duplicated results were removed by the EndNote software function.

Study selection and appraisal

Included articles were screened through three steps. Authors screened the title of articles. Indecently and irrelevant articles were excluded. Next, authors studied the abstract of the remaining articles, and irrelevant records also were excluded. Finally, the authors tried to achieve full texts of the articles. All processes had been done independently by the authors to diminish the risk of bias. Two researchers screened the studies separately by title and abstract to identify seemingly related articles for a second screening. Following this, two researchers independently examined the complete texts of the remaining papers and identified studies that met the inclusion and exclusion criteria for the review. Disagreements between the two researchers were resolved by discussion. If disagreements persisted, a third author reviewed the study and made the final decision. To increase the quality of the review, a blind method was used with the journal and author names hidden.

Data Extraction

Data extracted from each study included the first author's name, year of study, country of the population, number of the study population, age, gender, type of vitiligo, age of onset of vitiligo, systemic and cutaneous association, duration of disease, and family history of vitiligo.

Data analysis

The analysis was performed in Stata-14 using the "metan" command. Publication bias was assessed by the Begg's funnel plot based on the data of age of patients, family history, and type of vitiligo (segmental versus non-segmental), and Begg's and Egger's tests were also applied. Heterogeneity was assessed using the I-squared index and regarding its results, the meta-analysis was carried out by using the random-effects method. Forrest plots were drawn for variables of interest including age and gender. Subgroup analysis was performed just for a place (continent) and meta-regression was done to test the probable effect of time (year) and place (continent) on heterogeneity.

Results

Study characteristics

In this systematic review, 106 articles were found after searching PubMed (25 articles), Scopus (49 articles), and Web of Sciences (32 articles). The duplicated records then were removed by EndNote software and 41 articles remained. In the next step, after screening the titles, five irrelevant titles were omitted and 36 articles remained. Then the abstracts were evaluated by the authors and six articles with irrelevant abstracts were removed. In the final step, the full texts of remained articles were gathered and evaluated independently by the authors. Finally, 12 articles remained for final analysis. As mentioned, an explorer search was also conducted on google and five new articles were added. Hence, 17 articles were included in the final analysis. The PRISMA flowchart of the current study is shown in **Figure 1**.

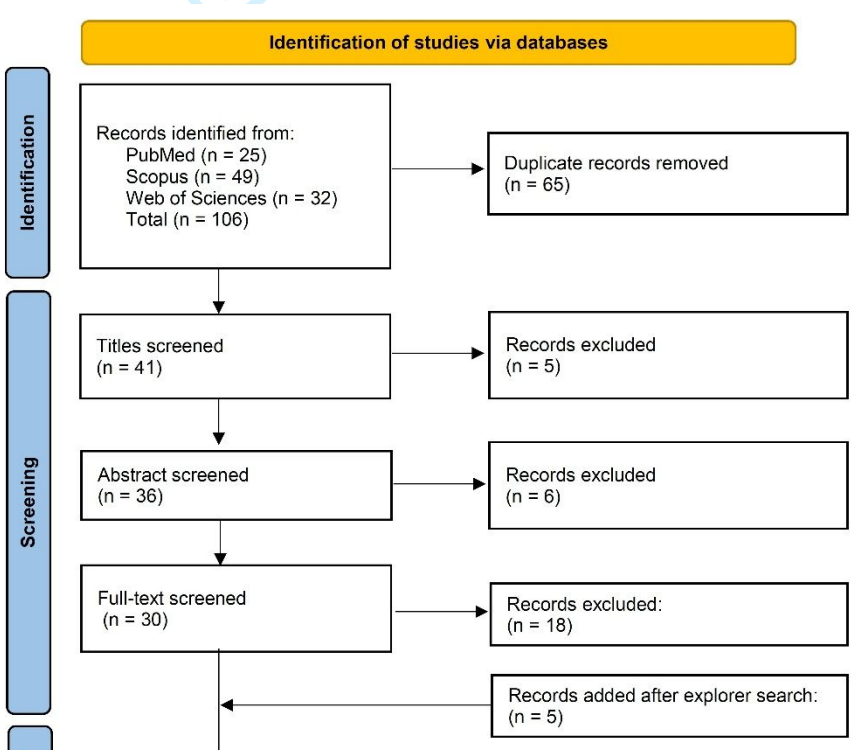

Figure 1. The PRISMA chart of the study.

These 17 articles were evaluated deeply by the authors and the risk of bias was assessed by the National Institutes of Health quality assessment tool. **supplement 1** shows the result of the risk of bias assessment.

The details of each study including the author's name, year of publishing, country, sample size, age, gender, type of vitiligo, and family history are summarized in **Table 1**. Concerning the country of study, 11 studies were from Asia (11-21), three from Europe (22-24), two from America (25, 26), and one from Africa (27).

Table 1. Overview of literature included in the meta-analysis

First Author	Year	Country	Sample size	Age Mean ± SD	Female/ Male	Segmental	Non-Segmental	Positive Family history
Halder (25)	1987	America	82	-	47/35	16	66	29
Hann (18)	1991	Korea	101	7.40±3.00	52/49	6	95	17
Jaisankar (19)	1992	India	90	-	55/35	19	71	3
Cho (15)	2000	Korea	80	-	41/39	26	53	11
Handa (17)	2003	India	625	6.72±3.00	357/268	29	596	76
Al-Mutairi (12)	2004	Kuwait	88	-	50/38	7	81	24
Mazereeuw-Hautier (23)	2010	France	114	-	61/53	25	89	-
Nicolaidou (24)	2010	Greece	123	-	81/42	8	118	45
Lin (20)	2011	China	620	7.57±3.00	318/302	160	460	84
Agarwal (11)	2012	India	268	6.00±3.00	152/116	45	223	65
Al-Refu (13)	2012	Jordan	71	6.80±3.00	33/38	4	67	11
Cavalcante (22)	2015	France	113	-	61/52	10	103	21
Farajzadeh (16)	2015	Iran	108	8.30±4.85	64/44	9	99	6
Martins (26)	2019	Brazil	701	5.90	439/262	200	501	82
Chauhan (14)	2020	India	579	9.18±4.08	304/275	15	564	53
EI-Husseiny(adol) (27)	2020	Egypt	123	11.49±3.63	81/42	5	118	10
EI-Husseiny(child) (27)	2020	Egypt	220	6.18±2.93	130/90	24	196	71
Zahra (21)	2022	India	256	7.88±4.13	149/107	37	219	49

Meta-analysis results

Table 2 present the clinical characteristic of childhood vitiligo in the world. The meta-analysis of 17 studies, including 4365 subjects demonstrated there were 2475 females (Estimated = 56.8%, 95% CI 54.45 - 59.22). Female to male ratio of 1.3:1 was identified in the present study (Estimated = 1.3, 95% CI 1.18 – 1.42) (Figure 3). Heterogeneity (I^2) was large in the female-to-male ratio, I2 = 73.7% (P<0.001). Therefore, we used meta-regression analysis to explore possible sources of heterogeneity. Meta-regression showed a significant association between continents and gender (P=0.038). The highest ratio was reported from Africa in one study (Estimated = 1.62, 95% CI 1.17-2.08) (**Figure 2**).

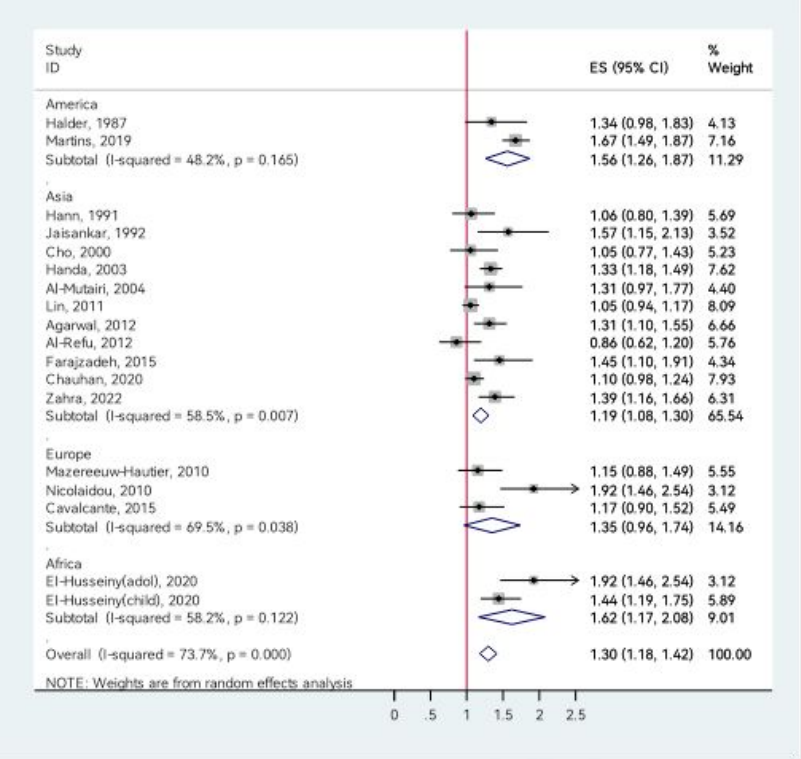

Figure 2. The forest plot of female to male ratio of patients with childhood vitiligo.

Age analysis was done on 9 studies involving 2971 vitiligo patients. The results showed that the mean age of patients was 7.47 years (Estimated 95% CI 5.41 – 9.52) (**Figure 3**).

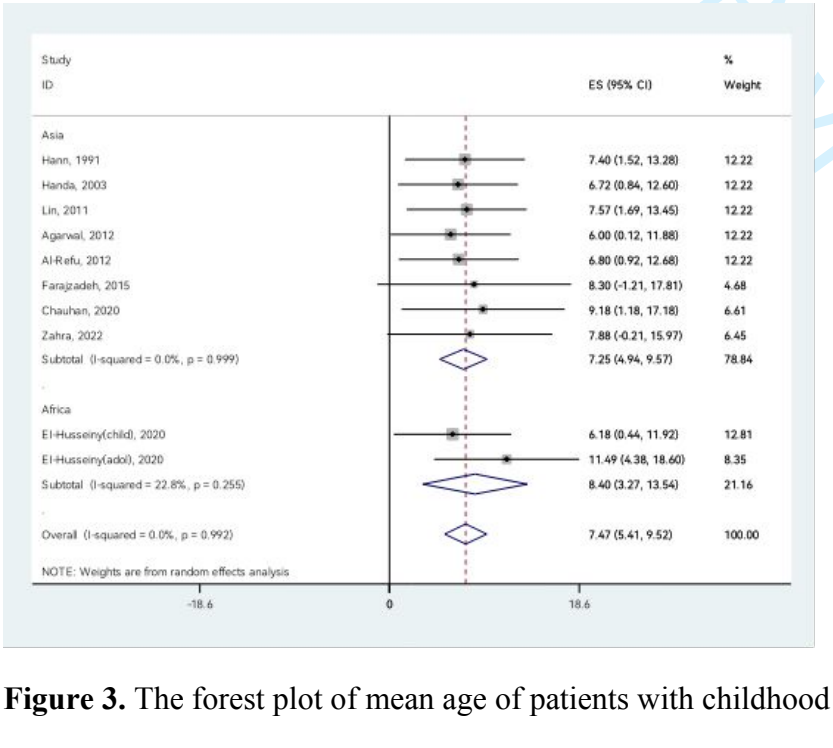

Figure 3. The forest plot of mean age of patients with childhood vitiligo.

The most common types of non-segmental vitiligo were Vulgaris (Estimated = 42.49 %, 95% CI 31.11 – 53.87), focal (Estimated = 27.21%, 95% CI 20.03 – 34.39), and acrofacial (Estimated = 17.8%, 95% CI 12.02 – 23.52) (**Table 2**).

Table 2. Clinical characteristics of childhood vitiligo in the world

Variables	N	% Estimated (95% CI)
Sex		
Male	1887	43.04 (40.58 – 45.50)
Female	2475	56.8 (54.45 - 59.22)
Type of vitiligo		
Segmental	645	13.3 (9.05 – 17.48)
Non-segmental	3719	86.7 (82.45 – 90.91)
Acrofacial	624	17.8 (12.02 – 23.52)
Universal	32	0.87 (0.28 – 1.46)
Mucosal	62	2.03 (1.04 – 3.02)
Focal	885	27.21 (20.03 – 34.39)
Vulgaris	1925	42.49 (31.11 – 53.87)
Mixed	26	3.38 (0.05 – 6.71)
Location of vitiligo		
Head and neck	893	49.35 (34.96 – 63.73)
Extremities	465	57.69 (28.92 – 86.45)
Trunk	131	28.22 (4.40 – 52.04)
Others (genitalia or mucosal)	34	4.80 (1.00 – 8.61)
Family history		
Positive	657	16.88 (13.37 – 20.39)
Site of the initial lesion		
Head and neck	1541	46.78 (41.66 – 51.89)
Extremities	1080	57.69 (28.92 – 86.45)
Trunk	479	15.62 (12.67 – 18.56)
Others (genitalia or mucosal)	160	6.04 (3.92 – 8.15)
Associations		
Atopy allergic	107	6.11 (3.08 – 9.14)
Halo Nevus	218	6.59 (4.05 – 9.13)
Alopecia Areata	46	1.08 (0.51 – 1.65)
Premature Canitis	54	4.97 (1.90 – 8.04)
Autoimmune diseases	22	1.76 (0.13 – 3.39)

Thyroid disorder	170	5.19 (3.54 – 6.83)
Anemia	89	5.84 (3.06 – 8.61)
Diabetes mellites	5	0.72 (-0.54 – 1.98)
Examination findings		
Kobner Phenomen	687	25.47 (18.64 – 32.29)
Leukotrichia	461	18.52 (14.05 – 22.99)
Precipitating factor		
Stress	651	27.41 (7.57 – 47.24)
Trauma	100	5.62 (4.20 – 7.03)
Others	59	3.67 (0.42 – 6.93)

Pooled non-segmental to segmental ratio was 4.6:1. I^2 was calculated as 83.8%. The lowest and highest ratios were noted in America with two studies (Estimated = 3.02, 95% CI 1.54 – 4.50) and Africa with one study (Estimated = 11.56, 95% CI -0.98 – 24.10), respectively (**Figure 4**). Using meta-regression, the association between continents and vitiligo type was insignificant (P=0.47).

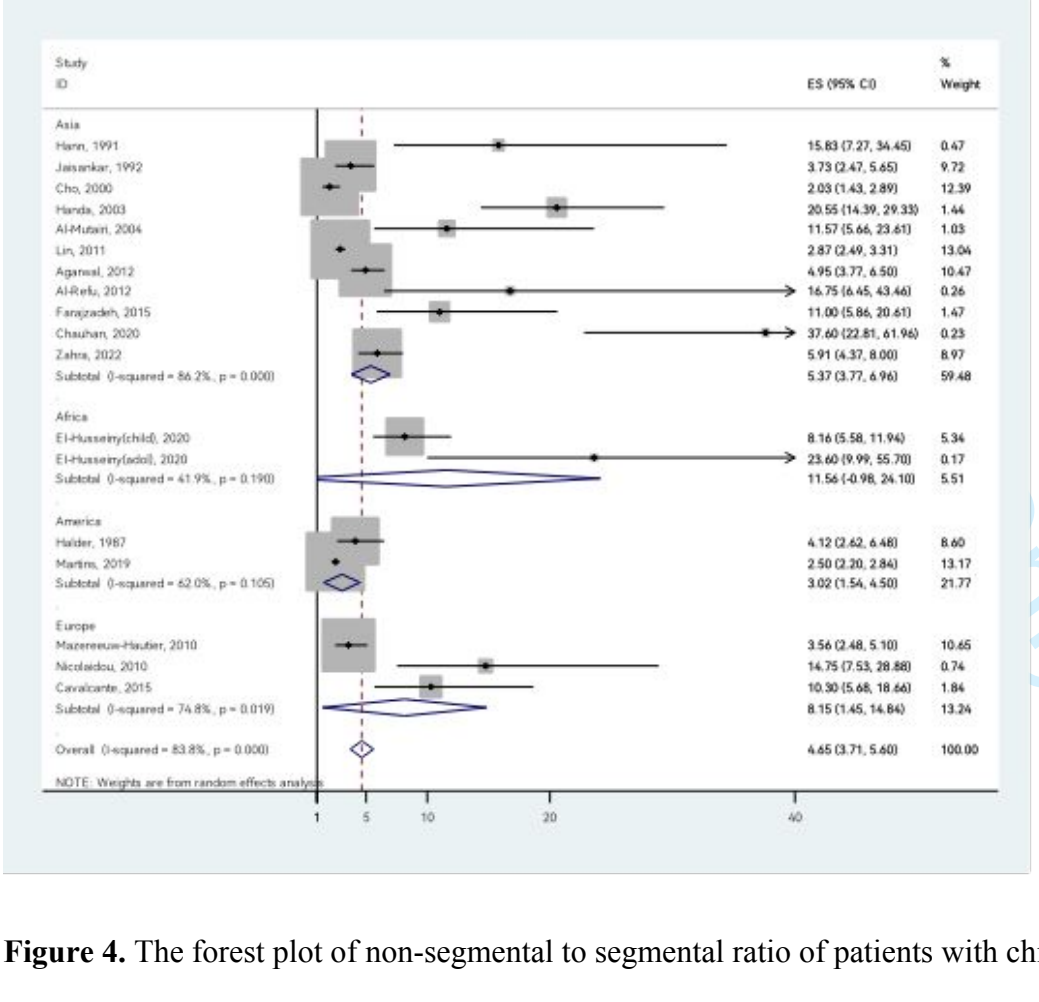

Figure 4. The forest plot of non-segmental to segmental ratio of patients with childhood vitiligo.

Positive family history was recorded in 657 patients with childhood vitiligo (Estimated = 16.88 %, 95% CI 13.37 – 20.39). Concerning the country of study, positive family history ranged from 13.91% (Asia with 11 studies) to 27.01% (Europe with 2 studies) (**Figure 5**). Using meta-regression, the association between continents and family history was not significant (P=0.11). The most common site of the initial lesion were extremities (57.69%), head/neck (46.78 %), and trunk (15.62 %). Kobner phenomena and leukotrichia were noted in 687 (Estimated = 25.47%, 95% CI 18.64 – 32.29) and 461 (Estimated = 18.52%, 95% CI 41.66 – 51.89) patients, respectively (**Table 2**).

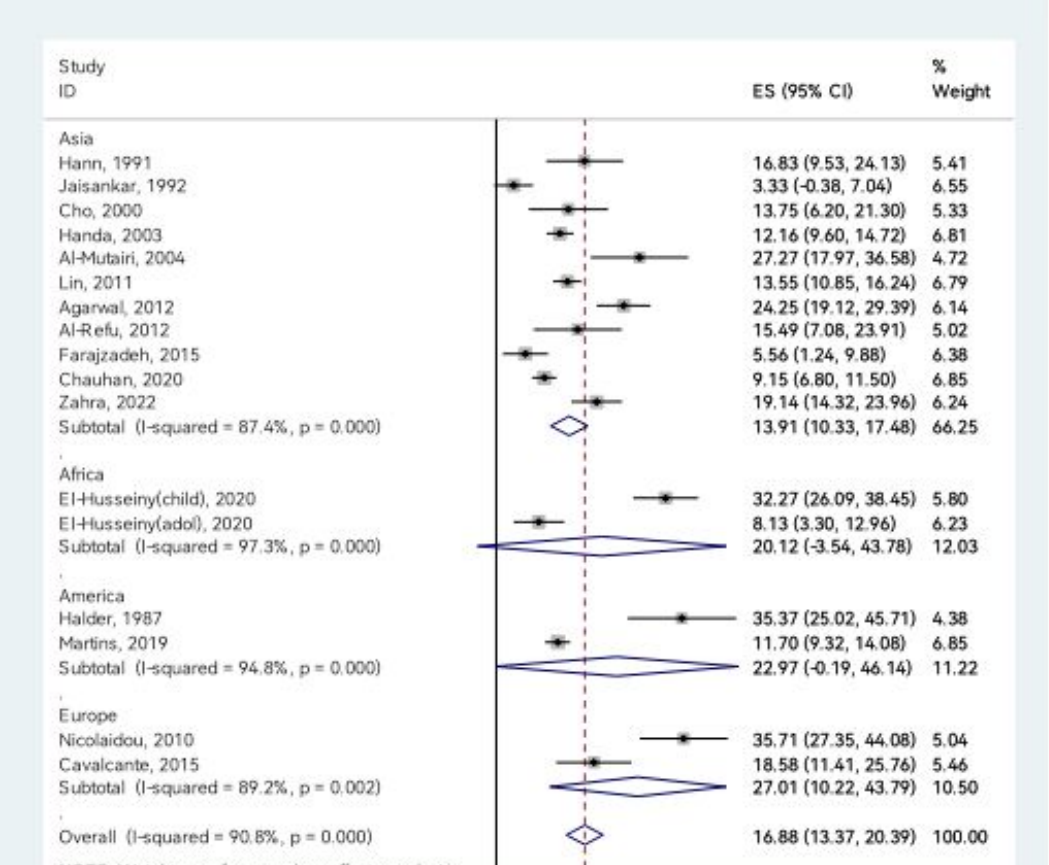

Figure 5. The forest plot of positive family history of vitiligo in patients with childhood vitiligo.

The most common cutaneous association in childhood vitiligo were Halo nevus (6.59%), Atopic and allergic diastasis (6.11%), premature canities (4.97%), and Alopecia areata (1.08%). The most common systemic associations were anemia (5.84%) and thyroid disorders (5.19%) (**Table 2**). The most common precipitating factors in patients with childhood vitiligo were stress

(Estimated = 27.41%, 95% CI 7.57 – 47.24) and trauma (Estimated = 5.62 %, 95% CI 4.20 – 7.03) (**Table 2**).

Publication bias

Visual inspection of Begg's funnel plot did not identify any substantial asymmetry among studies of childhood vitiligo and the age of patients. Egger's test (P=0.416) and Begg's (P=0.283) indicated no significant publication bias (**Figure 6**).

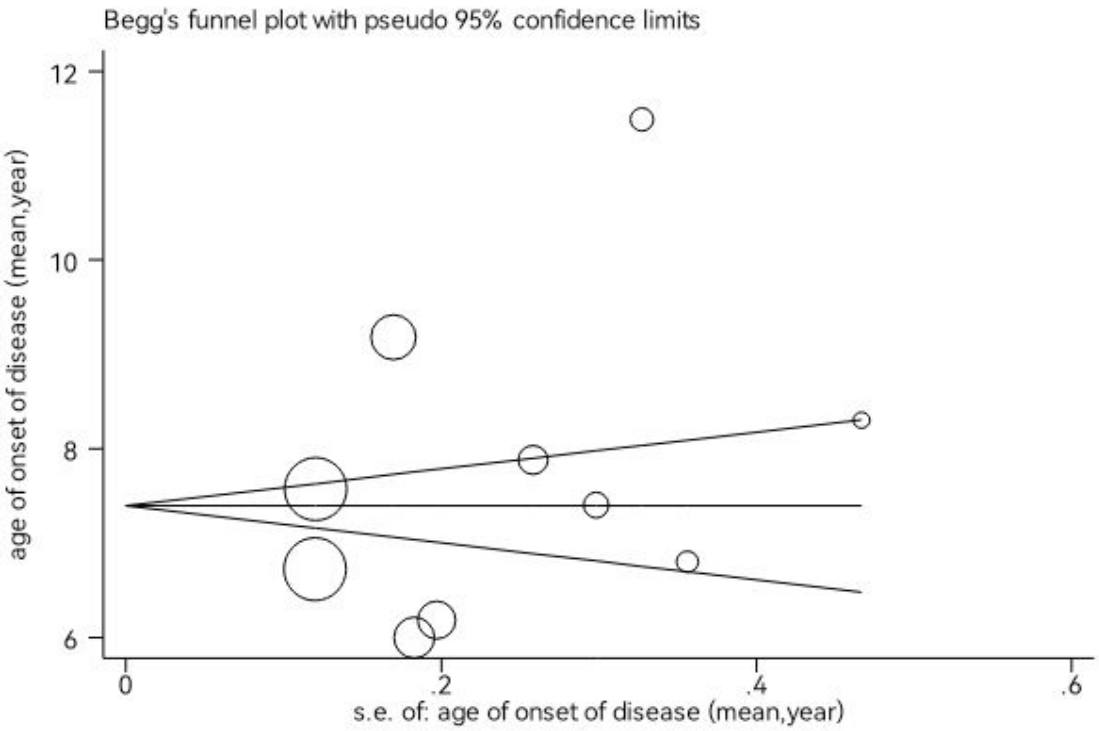

Figure 6. Begg's funnel plots of publication bias analyses

Discussion

In this study, the most clinical presentation of vitiligo in children was a school-aged girl with vitiligo vulgaris initiated from the head and neck with a positive family history in about 17% of cases and the possibility of association with anemia, thyroid disorders, and halo nevus.

According to the results of this meta-analysis, there was a female predominance over males (Female-to-male: 1.3: 1). However, a study by Cho et al. reported near equal incidence in both genders (15), and a study reported a reverse ratio (13). The higher occurrence of childhood vitiligo in females can be attributed to more prevalence of autoimmune conditions in the female gender and indirectly related to the increased stigma of the cosmetic appearance in vitiligo among the parents of the girl child and thus seek medical help may be sought earlier since generally vitiligo is considered as a cosmetic condition (21, 27).

Moreover, the results of the meta-regression analysis showed a significant association between the female predominance of childhood vitiligo and geographical area with a lower ratio in Asia and Europe than in Africa. In addition to different ethnicity in this area, increased public awareness about childhood vitiligo in more developed countries than in Africa may be the reason.

The results of the systematic analysis showed the prevalence of head and neck involvement as an initial lesion site is about fifty percent. Although the exact interpretation of data is difficult but more frequent exposure to the sun during playing, prone this site to develop vitiligo in genetically predisposed individuals (21, 27). Also, this site is more at the vision and evaluation. Extensive sun exposure induces high oxygen free radicals, which are detrimental to genetically predisposed melanocytes in vitiligo (28). Genital involvement was a less common site of involvement in children. This could be related to less active melanocytes under hormonal stimulation in children and less vulnerability to attack and also less friction and loss of melanocytes associated with sexual activity in children of the older age groups (29).

Vitiligo is sometimes preceded by some precipitating factors. The result of the current systematic review demonstrated stress and trauma were two common precipitating factors. The higher occurrence of trauma as a precipitating factor may be biased toward correlating the occurrence of vitiligo with a prior episode of any childhood trauma.

The most common cutaneous association in childhood vitiligo were halo nevus, atopic and allergic diastasis, and premature canities respectively.

Genetic factors are relevant in the pathogenesis of vitiligo (13, 23). So, positive family histories can be expected in children that are not related to ethnicity and are more relevant to personal genetic background.

Although the current study was the first systematic review and meta-analysis of the global geographic distribution of pediatric vitiligo, heterogeneity across studies represents an important limitation in combining observational studies for the current meta-analysis. We attempted to limit this heterogeneity through the use of relatively narrow inclusion criteria and assessing the quality of included studies via an NIH protocol. For the identified heterogeneity, we used meta-regression to explain potential sources of heterogeneity.

Although our study had some limitations, the strength of this review lies in its adherence to established methods for conducting systematic reviews, extensive searching, and a combined quality assessment of the included studies.

Finally compiling all available evidence on the clinico-epidemiologic pattern of childhood vitiligo will help for better identification of a clinical pattern of diseases, identification, and modification of possible related factors.

Conclusion and recommendations

Currently, there is no clear picture of the clinico-epidemiologic pattern of childhood vitiligo in the world, and this review details these characteristics of vitiligo in children. Although the gender differences vary between countries, the findings suggest that vitiligo is more common in girl children. Other findings such as the age of children, location of lesions, the pattern of vitiligo, and family history of vitiligo were similar in American, Asian, European, and African children.

Awareness of the typical pattern of childhood vitiligo in different geographic areas and its related factors in the world provides a better understanding of clinical disease identification and management. In the future, we recommend more studies from different geographic parts of the world and community settings for providing more reliable data.

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Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Statement of contribution: B.A.N and S.F designed the study and wrote the study protocol. B.A.N and F.R performed the study screening, selection, and data collection as first reviewer. M.M and F.P performed the statistical analysis and drafted the manuscript. M.K and S.F supervised the research work and was the third reviewer in case of discordance between B.A.N and F.R during study screening and selection. The manuscript was revised by M.K and S.F and M.M. All authors revised and approved the final version of this manuscript.

Data sharing statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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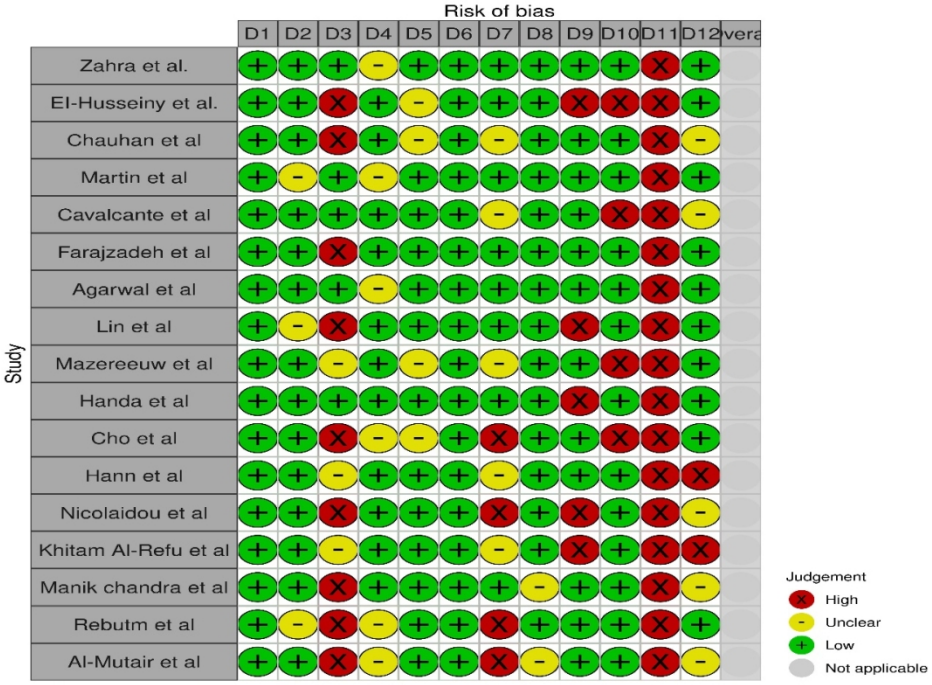

D1. Was the research question or objective in this paper clearly stated and appropriate?
D2. Was the study population clearly specified and defined?
D3. Did the authors include a sample size justification?
D4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
D5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
D6. Were the cases clearly defined and differentiated from controls?
D7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
D8. Was there use of concurrent controls?
D9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
D10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
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Global Clinico-epidemiologic Pattern of Childhood Vitiligo: A Systematic Review and Meta-Analysis

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Global Clinico-epidemiologic pattern of childhood vitiligo

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Global Clinico-epidemiologic Pattern of Childhood Vitiligo: A Systematic Review and Meta-Analysis

Abstract

Background: Childhood vitiligo differs from adult vitiligo in many aspects. To the best of the authors' knowledge, there is no systematic review of different clinico-epidemiologic patterns of vitiligo in children. This study aimed to review the characteristics of vitiligo among the pediatric population.

Methods: In June 2022, a comprehensive search was conducted using MeSh-based keywords on online databases including PubMed, Scopus, and Web of Sciences. The papers were assessed, and the eligible articles were selected. The selection of articles followed three distinct steps. The extracted clinico-epidemiological data were then imported into the STATA software for meta-analysis.

Results: The meta-analysis of 17 studies with 4365 subjects yielded 2475 females (estimated = 56.8%, 95% confidence interval [CI]: 54.45-59.22). The female-to-male ratio was determined to be 1.3:1. Meta-regression demonstrated a significant relationship between continents and gender (P = 0.03). The most prevalent types of non-segmental vitiligo were vulgaris (42.49%), focal (27.21%), and acrofacial (17.8%). The pooled ratio of non-segmental to segmental was 4.6:1. The highest and lowest ratios were found in Africa with one study (estimated = 11.56%, 95% CI: -0.98-24.10) and America with two studies (estimated = 3.02%, 95% CI: 1.54-4.50), respectively. Using meta-regression, the relationship between continents and vitiligo type was found to be insignificant (P = 0.47). Positive family history was recorded in 657 patients (estimated = 16.88%, 95% CI: 13.37-20.39). Positive family history varied by country of study from 13.91% (Asia with 11 studies) to 27.01% (Europe with two studies) (P=0.11). Kobner phenomena and leukotrichia were noted in 687 (25.47%) and 461 (18.52%) patients, respectively.

Conclusion: The review indicated that childhood vitiligo is more prevalent in females. Non-segmental forms of childhood vitiligo were the most common, including vulgaris, focal, and acrofacial. The clinico-epidemiologic pattern of childhood vitiligo is variable in different geographic areas.

Keywords: Childhood; Depigmentation; Epidemiology; Pediatric; Systematic Review; Vitiligo

Key messages

What is already known on this topic: Vitiligo is a life-altering condition. Childhood vitiligo differs from adult vitiligo in many aspects.

What this study adds: Vitiligo was most prevalent in Africa and more common in girls. The most frequent non-segmental vitiligo types were vulgaris (42.49%), focal (27.21%), and acrofacial (17.8%).

How this study might affect research, practice, or policy: Awareness of the typical pattern of childhood vitiligo in different geographic areas and its associated factors worldwide improves clinical disease identification and management.

Introduction

Vitiligo, an acquired autoimmune inflammatory disease of the skin, is a life-altering condition. The disease is primarily associated with significant cosmetic complaints and significant psychological effects, including the social stigma that lowers affected individuals' self-esteem (1).

Childhood vitiligo is different from adult vitiligo in many aspects (2), where negative experiences from childhood vitiligo may influence adult life (3). Recent studies in the United States showed that 1.9 million cases had been diagnosed with vitiligo, and its prevalence is 0.76 % (4). However, its prevalence varies from 0.5% to 2% in other countries (5). The exact prevalence of vitiligo in children is unknown, but at least 25% of cases begin before the age of 10 (6). Although vitiligo with a very early onset has been reported, the existence of true "congenital vitiligo" remains controversial (7).

The precise mechanism underlying vitiligo is not fully understood. Autoimmune, neurogenic, and self-destructive mechanisms are among the hypotheses reported (8). Exposure to environmental triggers such as trauma and sun exposure also have a significant role in vitiligo pathogenesis (9). Some studies also reported its association with other autoimmune diseases, including hypothyroidism, diabetes mellitus, alopecia, anemia, lupus, rheumatoid arthritis, and psoriasis. In addition, this disease is more prevalent among people with a positive family history of vitiligo (10).

Several characteristics distinguish childhood vitiligo from adult vitiligo, including a higher prevalence of segmental variant, a higher prevalence of halo nevi (HN), and a higher prevalence of a family history of autoimmune diseases. All races can be affected by childhood vitiligo, but the prevalence and pattern of the disease likely vary by geographic origin.

Understanding the clinico-epidemiologic characteristics of vitiligo in the pediatric population appears to correlate with positive treatment outcomes (7). Clinico-epidemiologic characteristics of pediatric vitiligo were described in several epidemiological studies. However, no comprehensive review exists in this regard. This study aimed to review the characteristics of vitiligo among the pediatric population through a systematic review and meta-analysis.

Methods

Literature search strategy

The present study is a systematic review and meta-analysis to evaluate the clinico-epidemiologic features of vitiligo in children. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was considered for this study. After consulting with experts in the fields of dermatology and pediatric dermatology, the MeSh databases were utilized to select keywords. The search was conducted on June 2022, where PubMed, Scopus, and Web of Sciences were searched. All databases were searched using the following queries limited to the title: ((vitiligo) AND (epidemiology OR Clinical OR characteristics)) AND (Child OR Pediatric OR Children OR Infants OR Neonate)). In addition, an exploratory, non-systematic Google search was conducted to locate any missed articles and grey literature.

Inclusion and exclusion criteria

Studies were eligible if they met all of the following inclusion criteria: (a) they were observational epidemiological studies; (b) they included patients with vitiligo under the age of 18. Conference articles, abstracts, protocols, narrative and systematic reviews, consensus opinions, and articles published in non-English languages were excluded from the study. No time limitation also was considered.

The records were imported into EndNote X8 software (V8.0.1. Clarivate Analytics). The duplicated results were removed through the EndNote software function.

Study selection and appraisal

Included articles were screened through three steps. Initially, the authors screened the title of the articles, unsuitable and irrelevant articles were excluded. Secondly, the authors studied the abstract of the remaining articles, and irrelevant records also were excluded. Finally, the authors attempted to retrieve the full texts of the articles. All processes were completed independently by the authors to diminish the risk of bias. Two researchers independently screened the studies by title and abstract to identify articles that appeared to be relevant for a second screening. Following this, two researchers independently examined the complete texts of the remaining papers and identified studies that met the inclusion and exclusion criteria for the review.

Disagreements between the two researchers were resolved through discussion. A third author reviewed the study and made the final decision if disagreements persisted. To improve the quality of the review, the journal and author names were concealed using a blind method.

Data Extraction

The extracted data from each study included the name of the first author, the year of the study, the country of the study population, the number of the study population, age, gender, type of vitiligo, age of onset of vitiligo, systemic and cutaneous association, disease duration, and family history of vitiligo.

Data analysis

STATA 14 was utilized to perform the analysis through the "metan" command. Begg's funnel plot was employed to assess publication bias based on patient age, family history, and type of vitiligo (segmental versus non-segmental). In addition, Begg's and Egger's tests were applied. Heterogeneity was assessed using the I-squared index, and the random-effects method was employed to conduct the meta-analysis of its results. Forrest plots were drawn for variables of interest, including age and gender. Subgroup analysis was conducted only for a specific location (continent), and meta-regression was performed to determine the probable effect of time (year) and location (continent) on heterogeneity.

Patient and public involvement

Patients and/or the public were not involved in this research's design, conduct, reporting, or dissemination plans.

Results

Study characteristics

In this systematic review, 106 articles were identified after searching PubMed (25 articles), Scopus (49 articles), and Web of Sciences (32 articles). The duplicated records were then removed via EndNote software, and 41 articles remained. After screening the titles, five irrelevant titles were omitted, leaving 36 articles. Then, the authors evaluated the abstracts, and six articles with irrelevant abstracts were removed. In the final step, the full texts of remained articles were gathered and evaluated independently by the authors. Finally, 12 articles remained for final analysis. As previously mentioned, a Google Explorer search was also performed, and five new articles were added. Consequently, 17 articles were included in the final analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the current study is shown in **Figure 1**. As mentioned in the method, non-English articles were excluded by using the language filter tool. There were five non-English articles, three of them were in Portuguese language, one was in French language, and one of them was in the Turkish language.

The authors thoroughly reviewed these 17 articles, and the risk of bias was assessed using the National Institutes of Health quality assessment tool. The outcome of the risk of bias assessment is shown in **Supplement 1**.

The details of each study, including the author's name, year of publishing, country, sample size, age, gender, type of vitiligo, and family history, are summarized in **Table 1**. Concerning the country of study, 11 studies were from Asia (11-21), three were from Europe (22-24), two from America (25, 26), and one from Africa (27).

Table 1. Overview of literature included in the meta-analysis

First Author	Year	Country	Sample size	Age Mean ± SD	Female/ Male	Segmental	Non-Segmental	Positive family history
America								
Halder (25)	1987	America	82	-	47/35	16	66	29
Martins (26)	2019	Brazil	701	5.90	439/262	200	501	82
Asia								
Hann (18)	1991	Korea	101	7.40±3.00	52/49	6	95	17
Jaisankar (19)	1992	India	90	-	55/35	19	71	3
Cho (15)	2000	Korea	80	-	41/39	26	53	11
Handa (17)	2003	India	625	6.72±3.00	357/268	29	596	76
Al-Mutairi (12)	2004	Kuwait	88	-	50/38	7	81	24
Lin (20)	2011	China	620	7.57±3.00	318/302	160	460	84
Agarwal (11)	2012	India	268	6.00±3.00	152/116	45	223	65
Al-Refu (13)	2012	Jordan	71	6.80±3.00	33/38	4	67	11
Farajzadeh (16)	2015	Iran	108	8.30±4.85	64/44	9	99	6
Chauhan (14)	2020	India	579	9.18±4.08	304/275	15	564	53
Zahra (21)	2022	India	256	7.88±4.13	149/107	37	219	49
Europe								
Mazereeuw-Hautier (23)	2010	France	114	-	61/53	25	89	-
Nicolaidou (24)	2010	Greece	123	-	81/42	8	118	45
Cavalcante (22)	2015	France	113	-	61/52	10	103	21
Africa								
EI-Husseiny(adol) (27)	2020	Egypt	123	11.49±3.63	81/42	5	118	10
EI-Husseiny(child) (27)	2020	Egypt	220	6.18±2.93	130/90	24	196	71

Meta-analysis results

The clinical characteristics of childhood vitiligo are presented in Table 2. The meta-analysis of 17 studies with 4365 subjects yielded 2475 females (estimated = 56.8%, 95% CI: 54.45-59.22). In the present study, a female-to-male ratio of 1.3:1 was identified (estimated = 1.3%, 95% CI: 1.18 – 1.42) (**Figure 3**). Heterogeneity (I^2) was large in the female-to-male ratio (I^2 = 73.7%: P<0.001). Therefore, we utilized meta-regression analysis to investigate potential heterogeneity sources. Meta-regression demonstrated a significant relationship between continents and gender

(P = 0.038). Africa was reported to have the highest ratio (estimated = 1.62%, 95% CI: 1.17-2.08) in one study (**Figure 2**).

Age analysis was performed in nine studies involving 2971 vitiligo patients. The results revealed that the average age of patients was 7.47 years (estimated =7.47, 95% CI: 5.41-9.52) (**Figure 3**).

The most common types of non-segmental vitiligo were vulgaris (estimated = 42.49%, 95% CI: 31.11–53.87), focal (estimated = 27.21%, 95% CI: 20.03-34.39), and acrofacial (estimated = 17.8%, 95% CI: 12.02-23.52) (**Table 2**).

Table 2. Clinical characteristics of childhood vitiligo worldwide

Variables	N	Estimated % (95% CI)
Sex		
Male	1887	43.04 (40.58 – 45.50)
Female	2475	56.8 (54.45 - 59.22)
Type of vitiligo		
Segmental	645	13.3 (9.05 – 17.48)
Non-segmental	3719	86.7 (82.45 – 90.91)
Acrofacial	624	17.8 (12.02 – 23.52)
Universal	32	0.87 (0.28 – 1.46)
Mucosal	62	2.03 (1.04 – 3.02)
Focal	885	27.21 (20.03 – 34.39)
Vulgaris	1925	42.49 (31.11 – 53.87)
Mixed	26	3.38 (0.05 – 6.71)
Location of vitiligo		
Head and neck	893	49.35 (34.96 – 63.73)
Extremities	465	57.69 (28.92 – 86.45)
Trunk	131	28.22 (4.40 – 52.04)
Others (genitalia or mucosal)	34	4.80 (1.00 – 8.61)
Family history		
Positive	657	16.88 (13.37 – 20.39)
Site of the initial lesion		
Head and neck	1541	46.78 (41.66 – 51.89)
Extremities	1080	57.69 (28.92 – 86.45)
Trunk	479	15.62 (12.67 – 18.56)
Others (genitalia or mucosal)	160	6.04 (3.92 – 8.15)
Associations		
Atopy allergic	107	6.11 (3.08 – 9.14)
Halo Nevus	218	6.59 (4.05 – 9.13)
Alopecia Areata	46	1.08 (0.51 – 1.65)
Premature Canitis	54	4.97 (1.90 – 8.04)
Autoimmune diseases	22	1.76 (0.13 – 3.39)
Thyroid disorder	170	5.19 (3.54 – 6.83)
Anemia	89	5.84 (3.06 – 8.61)
Diabetes mellites	5	0.72 (-0.54 – 1.98)
Examination findings		
Kobner Phenomen	687	25.47 (18.64 – 32.29)
Leukotrichia	461	18.52 (14.05 – 22.99)
Precipitating factor		

Stress	651	27.41 (7.57 – 47.24)
Trauma	100	5.62 (4.20 – 7.03)
Others	59	3.67 (0.42 – 6.93)

The pooled ratio of non-segmental to segmental was 4.6:1. I^2 was calculated to be 83.8%. Africa, with one study (estimated = 11.56%, 95% CI: -0.98-24.10), and America, with two studies (estimated = 3.02%, 95% CI: 1.54-4.50), had the highest and lowest ratios, respectively (**Figure 4**). Using meta-regression, the relationship between continents and vitiligo type was found to be insignificant (P = 0.47).

A positive family history was recorded in 657 patients with childhood vitiligo (estimated = 16.88%, 95% CI: 13.37-20.39). Positive family history varied by continent of study from 13.91% (Asia with 11 studies) to 27.01% (Europe with two studies) (**Figure 5**). Using meta-regression, the relationship between continents and family history was not statistically significant (P=0.11).

The most common initial lesion sites were the extremities (57.69%), head/neck (46.78%), and trunk (15.62%). Kobner phenomena and leukotrichia were observed in 687 (estimated = 25.47%, 95% CI: 18.64-32.29) and 461 (estimated = 18.52%, 95% CI: 41.66-51.89) patients, respectively (**Table 2**).

Halo nevus (6.59%), atopic and allergic diastasis (6.11%), premature canities (4.97%), and alopecia areata were the most common cutaneous associations in childhood vitiligo (1.08 %). Anemia (5.84%) and thyroid disorders (5.19 %) were the most prevalent systemic associations (**Table 2**). Stress (estimated = 27.41%, 95% CI: 7.57-47.24) and trauma (estimated = 5.62%, 95% CI: 4.20-7.03) were the most prevalent precipitating factors in patients with childhood vitiligo (**Table 2**).

Publication bias

A visual examination of Begg's funnel plot revealed no significant asymmetry between studies of childhood vitiligo and patient age. Both Egger's (P = 0.416) and Begg's (P = 0.283) tests indicated that there was no significant publication bias (**Figure 6**).

Discussion

In this study, the most common clinical presentation of vitiligo in children was a school-aged girl with vitiligo vulgaris initiated from the head and neck with a positive family history in about 17% of cases, and the possibility of association with anemia, thyroid disorders, and halo nevus.

According to the findings of this meta-analysis, females predominated over men (female-to-male: 1.3: 1). However, Cho et al. (15) reported a near-equal incidence in both sexes, and another study reported the opposite ratio (13). The higher incidence of childhood vitiligo in females can be attributed to the higher prevalence of autoimmune conditions in the female gender, which is indirectly related to the increased stigma of the cosmetic appearance in vitiligo among the parents of the girl child. As vitiligo is generally regarded as a cosmetic condition, medical attention may be sought earlier (21, 27).

In addition, the meta-regression analysis revealed a significant association between the female predominance of childhood vitiligo and geographical area, with a lower ratio in Asia and Europe than in Africa. In addition to differences in ethnicity, a greater awareness of childhood vitiligo in more developed countries than in Africa may be a contributing factor.

Approximately 50% of initial lesions occur in the head and neck, according to the results of the systematic analysis. However, the exact interpretation of the data is challenging, but more frequent sun exposure during sports increases the risk of vitiligo in genetically susceptible individuals (21, 27). Additionally, this site focuses more on vision and evaluation. Extensive sun exposure generates high levels of oxygen free radicals, which are detrimental to genetically susceptible melanocytes in vitiligo (28). Involvement in the genital region was less common among children. This may be due to less active melanocytes in children under hormonal stimulation, less vulnerability to attack, and less friction and loss of melanocytes associated with sexual activity in older children (29).

Vitiligo is sometimes preceded by some precipitating factors. According to the findings of the present systematic review, stress and trauma are two common precipitating factors. The higher

incidence of trauma as a precipitating factor may bias the correlation between vitiligo and a prior episode of childhood trauma.

The most prevalent cutaneous association in childhood vitiligo was halo nevus, followed by atopic and allergic diastasis and premature canities, respectively.

Genetic factors play an important role in the pathogenesis of vitiligo (13, 23). Therefore, positive family histories unrelated to ethnicity and more relevant to an individual's genetic background can be expected in children.

Heterogeneous studies pose a significant limitation in combining observational studies for the current meta-analysis. We attempted to reduce this heterogeneity by employing relatively narrow inclusion criteria and evaluating the quality of included studies using an NIH protocol. We utilized meta-regression to explain potential sources of the identified heterogeneity. Another limitation is that only English-language papers were included.

Despite some limitations, the strength of this review stems from its use of established methods for conducting systematic reviews, extensive searching, and a combined quality assessment of the included studies.

Finally, the compilation of all available evidence on the clinico-epidemiologic pattern of childhood vitiligo will help for better identification of a clinical pattern of disease and modifying potential risk factors.

Conclusion and recommendations

Currently, there is no clear picture of the clinico-epidemiologic pattern of childhood vitiligo worldwide. This article describes the clinical and epidemiologic characteristics of childhood vitiligo. Although gender disparities vary between countries, the findings indicate that vitiligo is more prevalent in female children. Other findings, such as the age of children, the location of lesions, the pattern of vitiligo, and family history of vitiligo, were similar in American, Asian, European, and African children.

Awareness of the typical pattern of childhood vitiligo in different geographic regions and its associated factors around the world improves clinical disease identification and management. To

provide more reliable data in the future, we suggest conducting additional research in diverse geographic regions and community settings.

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Patient and public involvement: Patients and/or the public were not involved in this research's design, conduct, reporting, or dissemination plans.

Statement of contribution: B.A.N. and S.F. designed the study and wrote the study protocol. As the first reviewer, B.A.N. and F.R. performed the study screening, selection, and data collection. M.M. and F.P. performed the statistical analysis and drafted the manuscript. M.K. and S.F. supervised the research work and was the third reviewer in case of discordance between B.A.N and F.R. during study screening and selection. M.K., S.F., and M.M. revised the manuscript. All authors revised and approved the final version of this manuscript.

Data sharing statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Figure Legends

Figure 1. The PRISMA chart of the study.

Figure 2. The forest plot of female to male ratio of patients with childhood vitiligo.

Figure 3. The forest plot of mean age of patients with childhood vitiligo.

Figure 4. The forest plot of non-segmental to the segmental ratio of patients with childhood vitiligo.

Figure 5. The forest plot of positive family history of vitiligo in patients with childhood vitiligo.

Figure 6. Begg's funnel plot of publication bias analyses.

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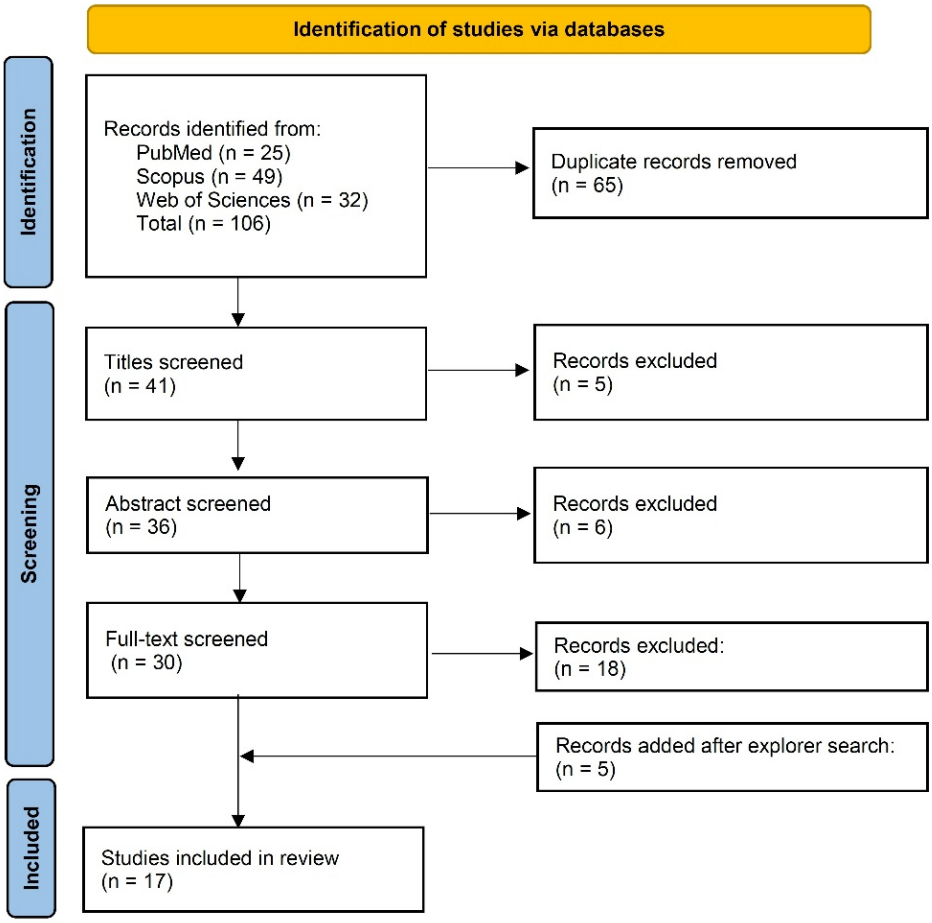

Figure 1. The PRISMA chart of the study.

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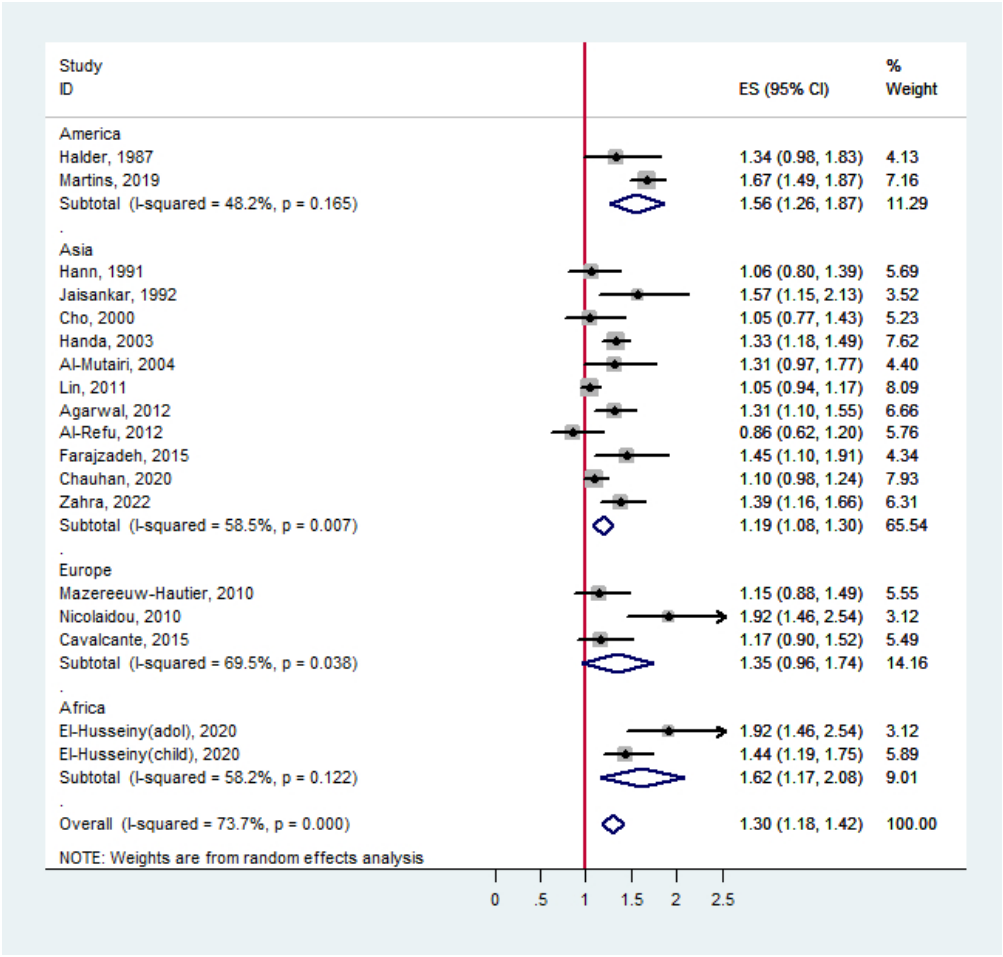

Figure 2. The forest plot of female to male ratio of patients with childhood vitiligo.

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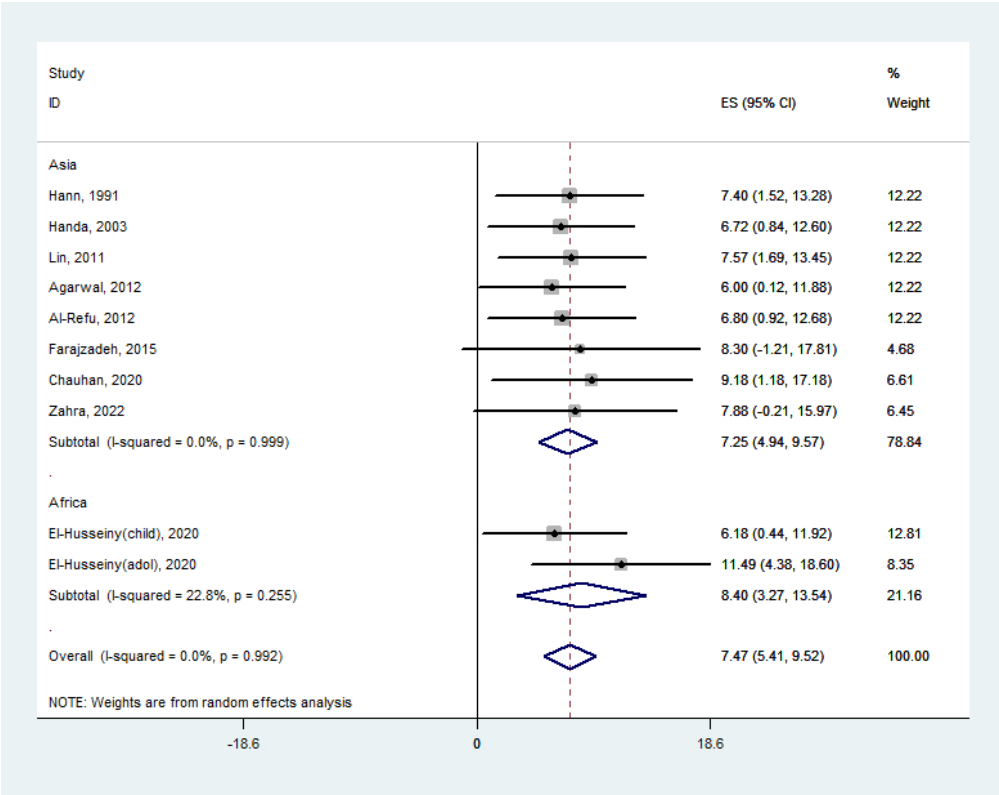

Figure 3. The forest plot of mean age of patients with childhood vitiligo.

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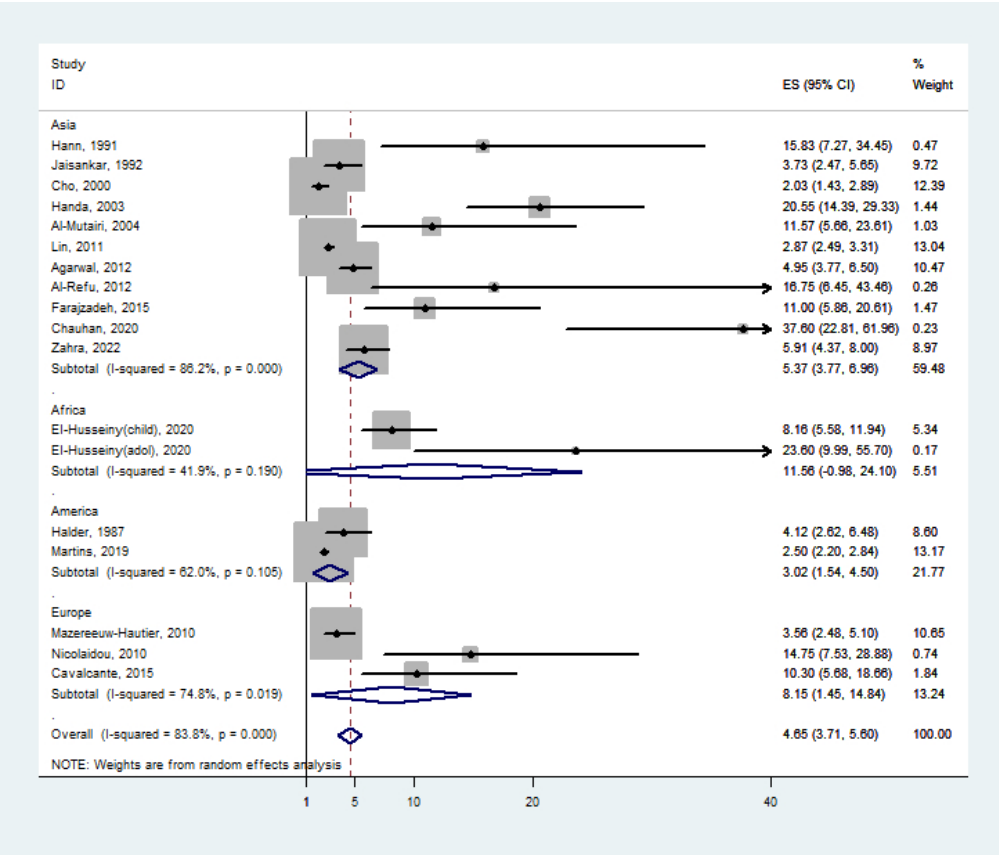

Figure 4. The forest plot of non-segmental to the segmental ratio of patients with childhood vitiligo.

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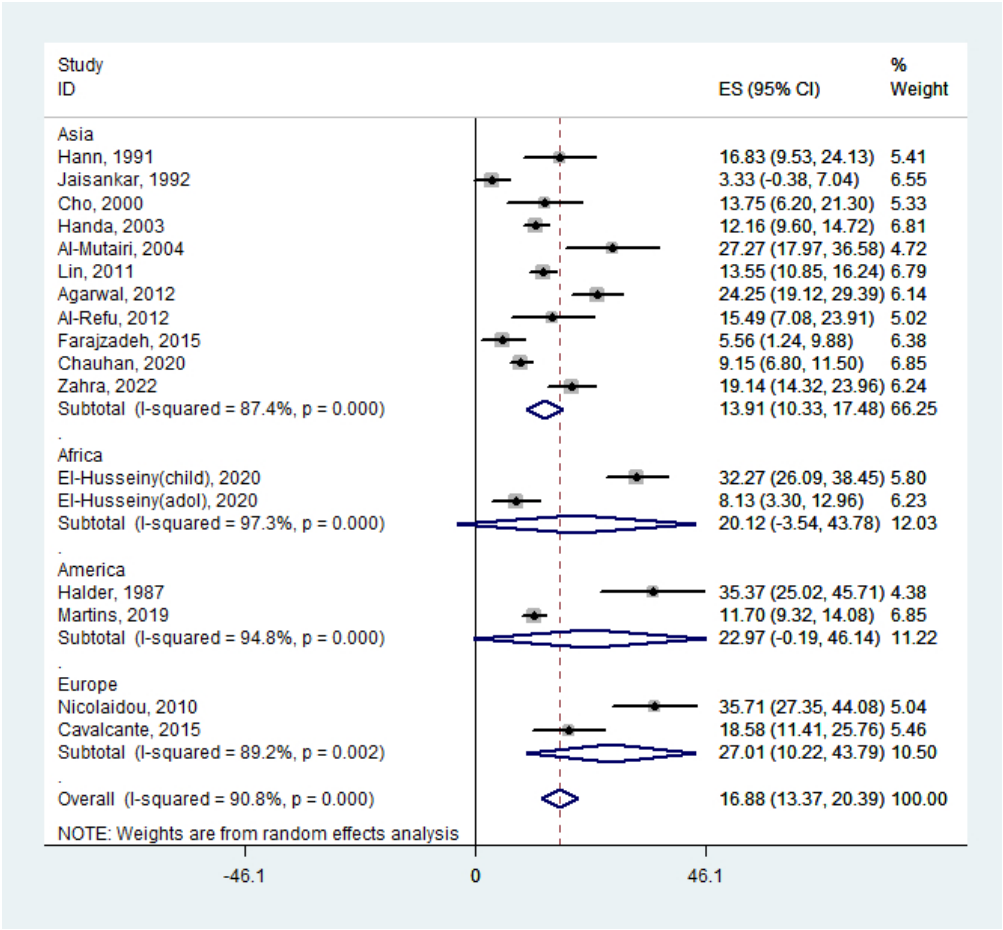


Figure 5. The forest plot of positive family history of vitiligo in patients with childhood vitiligo.

234x216mm (72 x 72 DPI)

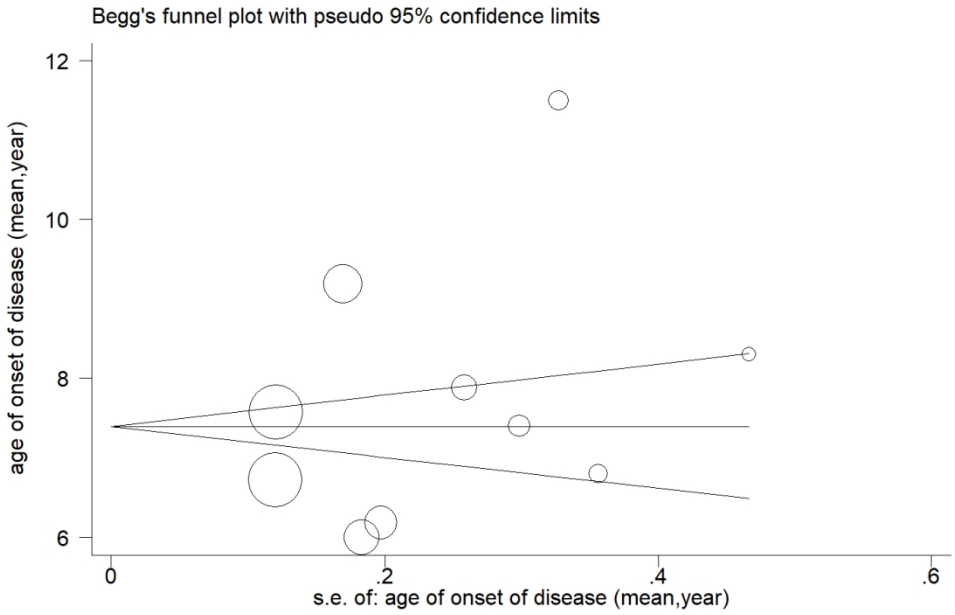
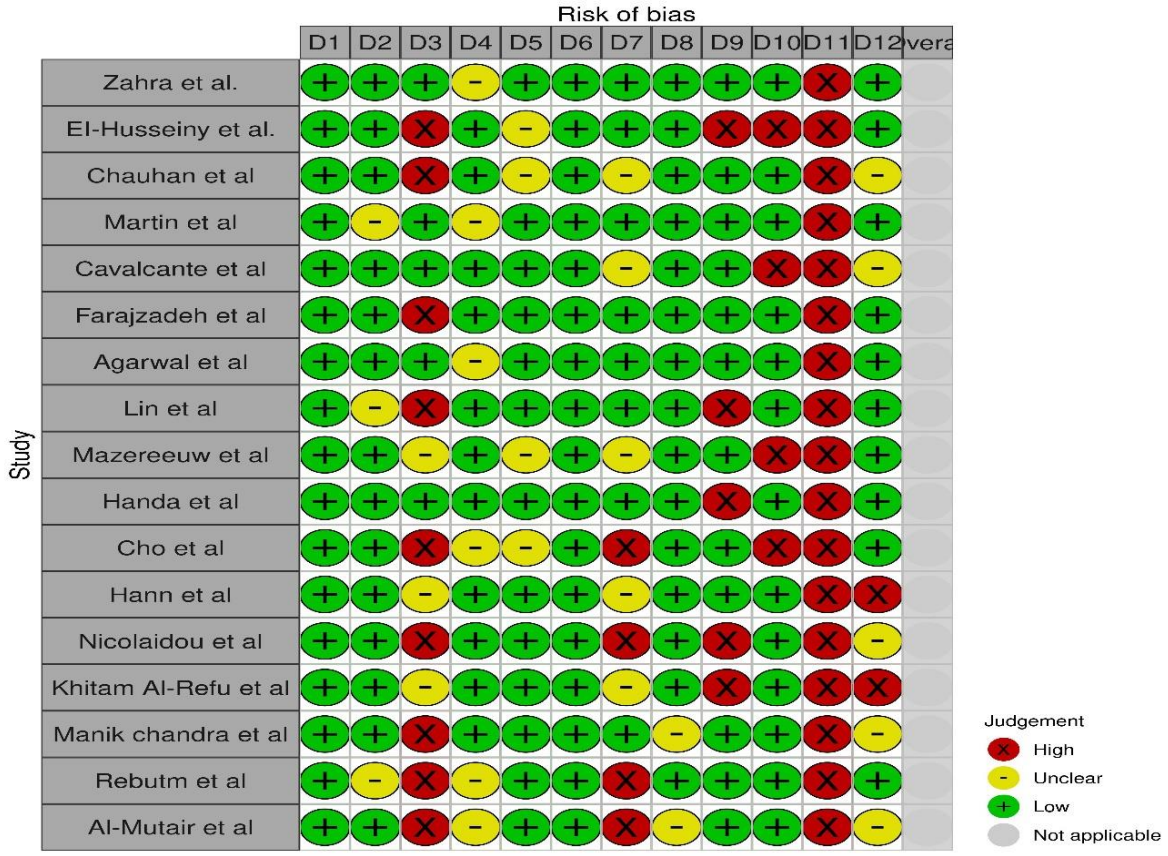


Figure 6. Begg's funnel plot of publication bias analyses.

977x651mm (38 x 38 DPI)



D1. Was the research question or objective in this paper clearly stated and appropriate?
D2. Was the study population clearly specified and defined?
D3. Did the authors include a sample size justification?
D4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
D5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
D6. Were the cases clearly defined and differentiated from controls?
D7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
D8. Was there use of concurrent controls?
D9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
D10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
D11. Were the assessors of exposure/risk blinded to the case or control status of participants?
D12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?