Review Article

Epidemiology of Recurrent Herpes Labialis: A Prevalence Meta-analysis

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Abstract

Recurrent herpes labialis (RHL) is a highly prevalent lesion and is one of the most common human viral infections worldwide. The aim of this study was to determine the pooled prevalence of RHL worldwide and in different continents, distinguishing between child and adult populations. A search for studies on RHL epidemiology was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science, and Scopus. The estimation of the pooled proportion was carried out with the generic inverse variance method, using the standard error of the proportion with 95% confidence intervals. Twenty-eight studies with 143,513 participants were included in this meta-analysis. The pooled prevalence of RHL worldwide was 14%, with 3% observed in the pediatric population and 17% in the adult population. By continent, the pooled prevalence of RHL was, in decreasing order, 21% in North America (nine studies), 15% in Africa (two studies), 14% in South America (five studies), 13% in Europe (twelve studies), and 7% in Asia (four studies). RHL is a very common condition, affecting approximately 1 in 7 people. RHL manifests at a significantly higher frequency in the adult population than in the pediatric population.

Keywords: Epidemiology, geographic locations, herpes labialis, herpes simplex

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Introduction

There are two main types of herpes simplex virus (HSV): HSV-1 and HSV-2. HSV-1 is primarily associated with oral infections, while HSV-2 is mainly associated with genital infections. Recurrent herpes labialis (RHL) is characterized by the reactivation of the latent type 1 HSV (HSV-1).[1] RHL manifests as an episode or outbreak distinguished by the presence of small, clustered vesicles on the labial semi-mucosa and the surrounding labial skin.[2] The seroprevalence of HSV-1 antibodies in the global population is notably high, ranging from 35% to 65% across diverse studies. Consequently, RHL has been identified as a prevalent lesion (~20%) and is recognized as one of the most common human viral infections worldwide. The average incidence of RHL is estimated to be approximately 1.6 per 1000 patients per year, with a prevalence of 2.5 per 1000 patients, though this varies significantly between countries and different geographical areas, with a higher frequency observed in females.[3]

RHL is typically triggered by various factors, including stress, previous local trauma, menstruation or hormonal changes in women, febrile infectious diseases, and sunlight exposure. The frequency of these recurrent outbreaks exhibits significant inter-individual variability, resulting in substantial psychosocial consequences for patients experiencing persistent or continuous outbreaks. The progression of RHL occurs in several stages, with the precursor stage characterized by the onset of prodromal

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symptoms, including perceptions of pain, tingling, or burning in the affected area.[4] This is followed by the appearance of a "cluster" of vesicle-like lesions. Rupture of the vesicles leads to crusting in the final phase of the lesions, leading to healing without scarring. The duration of this final phase is reported to be 7–10 days.[5] This study aimed to ascertain the pooled prevalence of RHL worldwide and on several continents, differentiating between child and adult populations.

Materials and Methods

The present study adhered to the guidelines for publishing Protocols for Systematic Reviews and Meta-Analyses version 2020.[6]

Search strategy

A search was conducted for studies on the epidemiology of RHL up to November 2024 in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and Scopus. For the grey literature, the search tool Google Scholar has also been used. Search strategies were developed for each database using a combination of Medical Subjects Headings (MeSH) and free text terms. The search terms were: "herpes labialis/statistics and numerical data"[MeSH Terms] OR ("herpes labial*" AND "epidemiology"[MeSH Terms]); "herpes labial*" AND "epidemiology;" TITLE-ABS-KEY ("herpes labial*" AND "epidemiology"). The inclusion criteria were as follows: (a) all prevalence studies related to our purpose, (b) articles without relevant risk of bias (RoB) that reached up to 55.6% or more (moderate–low RoB) on the Joanna Briggs Institute (JBI) checklist for prevalence studies),[7] and (c) articles written in any language and with no restrictions on publication date. The exclusion criteria were: (a) articles without full-text availability, (b) articles without clinical data, and (d) studies with nonusable data.

Assessment of methodological quality

The methodological quality of the studies and the RoB was screened using the JBI checklist for prevalence studies[7] that considered nine questions: 1) Was the sample frame appropriate to address the target population?; 2) Were study participants sampled in an appropriate way?; 3) Was the sample size adequate?; 4) Were the study subjects and the setting described in detail?; 5) Was the data analysis conducted with sufficient coverage of the identified sample?; 6) Were valid methods used for the identification of the condition?; 7) Was the condition measured in a standard, reliable way for all participants?; 8) Was there appropriate statistical analysis?, and 9) Was the response rate adequate, and if not, was the low response rate managed appropriately? Each question was categorized as "Yes" (low RoB), "Unclear" (moderate RoB), and "No" (High RoB). A number of 'yes' answers ≤4 (44.4%) determined that the study was classified as having a high RoB, a number of 'yes' answers between 5 (55.6%) and 6 (66.7%) was classified as having a moderate RoB, and a number of 'yes' answers ≥7 (77.8%) was classified as having a low RoB.

Data extraction

The pooled prevalence of RHL was determined worldwide and by continent (Europe, North America, South America, Asia and Africa). The pooled prevalence of RHL was also established, distinguishing between pediatric and adult populations.

Statistical analysis

For the meta-analysis, data were processed with Review Manager version 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark). The proportion (P) was calculated by dividing the number of positive cases (n) by the total population (N). Estimation of the proportion was carried out with the generic inverse of variance method, using the standard error of the proportion (SE) and 95% confidence intervals (95% confidence interval (CI). The SE was obtained according to the formula SQRT ($P \times (1 - P)/N$). Heterogeneity was determined according to the Higgins statistic (I^2). The minimum level of significance was set at a $P < 0.05$.

Results

Study selection

In the initial search, 282 articles were identified (86 in PubMed, 100 in WoS, and 96 in Scopus) between 1960 and 2018, 79 of them duplicates, leaving 203 articles for eligibility. One hundred and seventy-five studies were excluded due to (a) articles with no full-text availability (n = 55), (b) articles without clinical data (n = 41), and (c) studies with nonusable data (n = 79). After applying these criteria, 28 studies were included in this meta-analysis [Figure 1].

Study characteristics

Table 1 presents the main descriptive characteristics of the 28 studies with 143,513 participants were considered in this prevalence meta-analysis.[8-35] Study populations from Europe (n = 12), North America (n = 9), South America (n = 5), Asia (n = 4), and Africa (n = 2) were included. Demographic data, prevalence rate, and type of population studied were also incorporated.

Risk of bias

The RoB of the 28 studies analyzed is shown in Table 2. Three studies (10.7%)[16,17,27] were classified as low RoB and 25 (89.3%)[8-15,18-26,28-35] as moderate RoB.

Prevalence of recurrent herpes labialis globally and by continent

Figure 2 shows the pooled prevalence of RHL globally and by continent. Twenty-eight studies[8-35] that included 143,513 participants [Figure 2] found a pooled overall RHL prevalence of 14% (95% CI: 12%–16%). Study variability ranges from a maximum pooled RHL prevalence of 45% (95% CI: 39%–51%)[9] to a minimum pooled RHL prevalence of 0.2% (95% CI: −0.1%-0.3%).[26]

Twelve studies[10,11,17,21-24,28,29,31,33,35] involving 67,820 participants determined the pooled prevalence of RHL in Europe [Figure 2a]. The pooled RHL prevalence in the

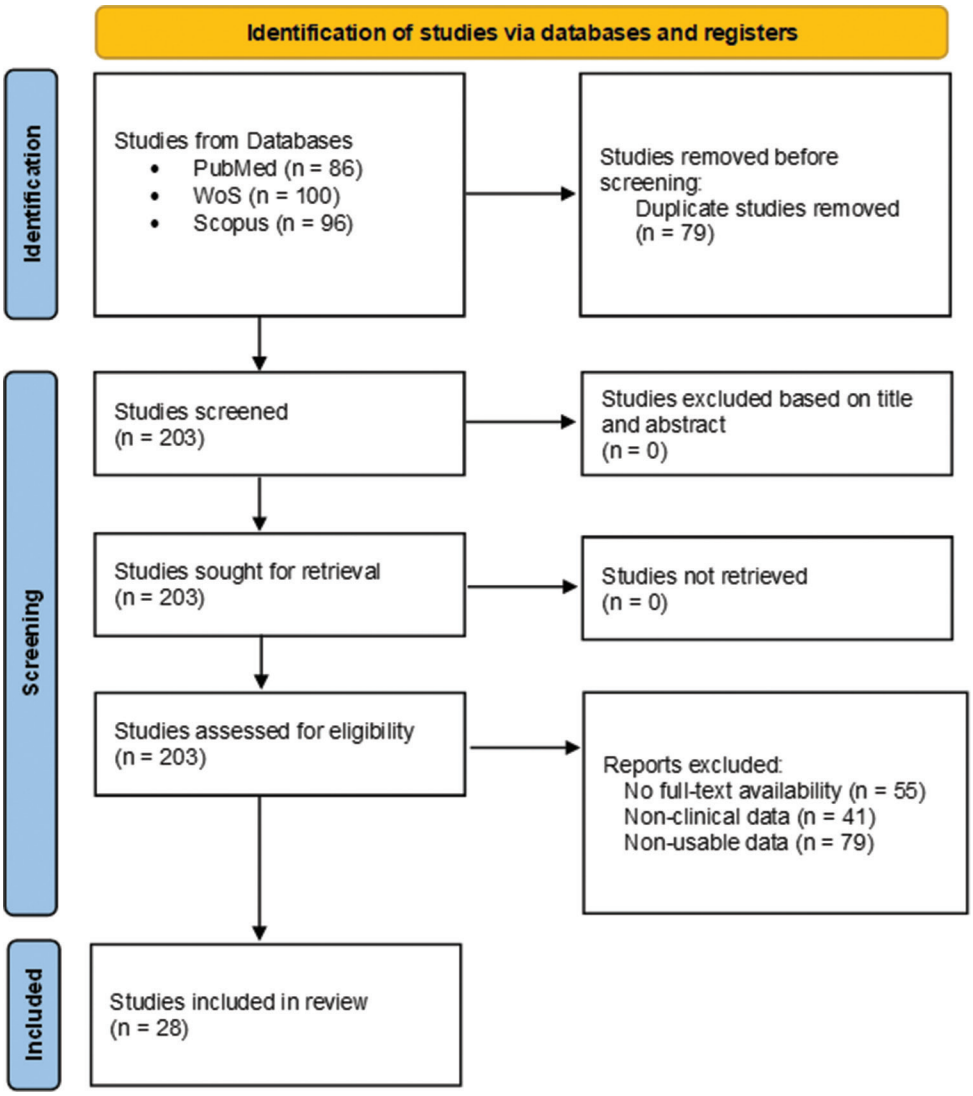

Figure 1: Flow diagram of study selection

European population was 13% (95%CI: 9%–16%). Nine studies[8-10,12,13,15,18,27,30] with 63,680 subjects established the pooled RHL prevalence in North America [Figure 2b]. The pooled RHL prevalence in Americans was 21% (95%CI: 17%–24%). Five studies[10,14,25,26,34] involving 5414 participants specified the pooled prevalence of RHL on the South American continent [Figure 2c]. The pooled RHL prevalence in South Americans was 14% (95%CI: 7%–20%). Four studies[10,16,20,32] with 5144 subjects reported the pooled RHL prevalence in Asia [Figure 2d]. The pooled RHL prevalence in the Asian population was 7% (95%CI: 2%–13%). Finally, two studies[10,19] covering 1455 subjects set the pooled prevalence of RHL in Africa [Figure 2e]. The pooled RHL prevalence in the African population was 15% (95%CI: −13%–44%).

Prevalence of recurrent herpes labialis in pediatric and adult populations

Six studies,[14,18,23,25,29,31] which considered 9382 participants, established the prevalence of RHL in the pediatric population [Figure 3a]. The pooled RHL prevalence in the pediatric population was 3% (95%CI: 2%–4%). Twenty-two studies[8-13,15-17,19-22,24,26-28,30,32-36] involving 53,980 adults specified the prevalence of RHL in the adult population [Figure 3b]. The pooled RHL prevalence in the adult population was 17% (95% CI 14%–20%).

Discussion

The present meta-analysis on the epidemiology of RHL included data from 28 studies.

RHL is very common and is one of the most common human viral infections worldwide. RHL is caused by the reactivation of the HSV, usually HSV-1. The condition presents with episodes of small vesicles located on the labial semi-mucosa and surrounding skin. Following the initial outbreak, the virus disseminates to the sensory nerve cells, where it remains latent. The reactivation of HSV on the lips is often triggered by various factors, including infectious febrile processes, stress, trauma, menstruation or hormonal changes in women,

sunlight or ultraviolet rays, and certain drugs. This can have significant psychosocial consequences for patients who suffer continuous recurrences.[5]

In this study, the pooled prevalence of RHL worldwide was 14%. By continent, the highest pooled RHL prevalence was observed in North America, followed by Africa, South America,

Table 1: Descriptive characteristics of the twenty-eight studies included in this meta-analysis

Study, year	Study population (demographic data)*; geographical origin	Prevalence, *n/N* (%)	Type of population
Ship *et al*., 1960[8]	300 (nr); North America	15/300 (5)	Health sciences college students
Ship *et al*., 1967[9]	343 (21.7 years); North America	108/343 (31.5)	Health sciences college students and hospital patients
	242 (36.5 years); North America	108/242 (44.6)	
Embil *et al*., 1975[10]	4155 (nr); North America	1670/4155 (40.2)	Health sciences college students
	2085 (nr); Europe	646/2085 (31.0)	
	1713 (nr); South America	273/1713 (15.9)	
	1502 (nr); Asia	347/1502 (23.1)	
	404 (nr); Africa	122/404 (30.2)	
Axéll, 1976[11]	18659 (nr); Europe	2612/18,659 (14.0)	Swedish population
Young *et al*., 1976[12]	1031 (nr); North America	211/1031 (20.5)	Health sciences college students
Ship *et al*., 1977[13]	651 (nr); North America	156/651 (23.9)	Health sciences college students
Crivelli *et al*., 1988[14]	331 (nr); South America	44/331 (13.3)	Schoolchildren (4—13 years)
Young *et al*., 1988[15]	446 (nr); North America	147/446 (32.9)	Blood donors
Axéll *et al*., 1990[16]	234 (104 males, 130 females; 33.8 years); Asia	13/234 (5.6)	Dental college students
	233 (137 males, 96 females; 31.0 years); Asia	6/233 (2.6)	
Axéll and Liedholm, 1990[17]	20,333 (43.0 years); Europe	652/20,333 (3.2)	Adult Swedish population
Kleinman *et al*., 1994[18]	40,693 (nr); North America	323/40,693 (0.8)	School children (5–17 years)
Arendorf and van der Ross, 1996[19]	1051 (nr); Africa	8/1051 (0.7)	Preschool population
Darwazeh and Pillai, 1998[20]	2175 (1190 males, 985 females); Asia	64/2175 (2.9)	Outpatients of dental college clinic
Kovac-Kovacic and Skaleric, 2000[21]	555 (263 males, 292 females); Europe	89/555 (16.0)	General population
Reichart, 2000[22]	2022 (907 males, 115 females); Europe	28/2022 (1.4)	General population
Garcia-Pola *et al*., 2002[23]	624 (307 males, 317 females); Europe	10/624 (1.6)	Child population (6 years)
Löwhagen *et al*., 2002[24]	3523 (nr); Europe	937/3523 (26.6)	Swedish population
Bessa *et al*., 2004[25]	1211 (571 males, 640 females); South America	10/1211 (0.8)	Child population (0–12 years)
Dos Santos *et al*., 2004[26]	587 (289 males, 298 females); South America	1/587 (0.2)	Amazonian Indian population
Shulman, 2004[27]	10,032 (4934 males, 5098 females); North America	143/10,032 (1.4)	General population
Lorette *et al*., 2006[28]	9342 (4335 males, 5007 females); Europe	1419/8342 (15.2)	General population
Parlak *et al*., 2006[29]	993 (534 males, 459 females; 14.2 years); Europe	29/993 (2.9)	Students (13–16 years)
Parks *et al*., 2007[30]	5787 (2888 males, 2899 females); North America	913/5787 (15.7)	General population
Majorana *et al*., 2010[31]	10,128 (5874 males, 4254 females); Europe	271/10,128 (2.7)	Child population (0–12 years)
Sawair *et al*., 2010[32]	1000 (373 males, 627 females); Asia	23/1000 (2.3)	College students
Celik *et al*., 2013[33]	333 (68 males, 265 females); Europe	13/333 (3.9)	Health sciences college students
Barrientos Sánchez, 2014[34]	1572 (542 males, 1030 females; 22.9 years); South America	609/1572 (38.7)	General population
Perrotta, 2020[35]	223 (214 males, 9 females; 39.1 years); Europe	78/223 (34.9)	Elite mountain bikers

*Gender distribution; mean age. *n/N*: Number of RHL patients/total sample size, nr: Data not reported, RHL: Recurrent herpes labialis

Europe, and finally Asia, which exhibited the lowest pooled RHL prevalence.

On the North American continent, the pooled RHL prevalence reached 21%. Of the nine studies that considered this population, four studies,[10,12,18,27] reported much lower percentages (≤4%), while two studies,[9,15] communicated much higher percentages (≥31%).

In Africa, the pooled RHL prevalence was 15%. Only two studies[10,19] looked at the African population and found very different percentages.

In South America, the pooled prevalence of RHL was 14%. Of the five studies that focused on the South American population, two[25,26] reported very low prevalences (≤1%), while one study[34] found a much higher pooled RHL prevalence in this population (39%).

In Europe, the pooled prevalence of RHL was 13%. Of the twelve studies evaluating the European population, six studies,[17,22,23,29,31,33] reported much lower prevalences (≤4%), whereas three studies,[10,24,35] reported much higher prevalences (≥27%).

In Asia, the pooled prevalence of RHL was 7%. Of the four studies that evaluated the Asian population, three,[16,20,32] found lower percentages (≤3%), while one study,[10] reported a much higher percentage (23%).

The observed variations in the prevalence of RHL across different continents are hypothesized to be attributable to the distinct characteristics of the study populations. RHL has been identified as a significant health concern, with affected individuals requiring therapeutic interventions to enhance their quality of life. There is a pervasive lack of awareness

Table 2: Assessment of the methodological quality of studies reporting prevalence data using the Joanna Briggs Institute checklist

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total (%)	RoB
Ship, 1960[8]	No	No	Yes	Yes	Yes	No	Yes	No	Yes	55.6	Moderate
Ship, 1967[9]	No	No	Yes	Yes	Yes	No	Yes	No	Yes	55.6	Moderate
Embil, 1975[10]	No	No	Yes	Yes	Yes	No	Yes	No	Yes	55.6	Moderate
Axell, 1976[11]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	66.7	Moderate
Young, 1976[12]	No	No	Yes	Yes	Yes	No	Yes	No	Yes	55.6	Moderate
Ship, 1977[13]	No	No	Yes	Yes	Yes	Yes	Yes	No	No	55.6	Moderate
Crivelli, 1988[14]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	66.7	Moderate
Young, 1988[15]	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	55.6	Moderate
Axell, 1990[16]	No	No	Yes	Yes	Yes	Yes	Yes	No	No	66.7	Moderate
Axell, 1990[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	77.8	Low
Kleinman, 1994[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	77.8	Low
Arendorf, 1996[19]	No	Yes	Yes	Yes	Yes	Questionable	Yes	No	No	55.6	Moderate
Darwazeh, 1998[20]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	66.7	Moderate
Kovac-Kavcic, 2000[21]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	66.7	Moderate
Reichart, 2000[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	66.7	Moderate
Garcia-Pola, 2002[23]	No	Yes	Yes	Yes	Yes	Questionable	Yes	No	No	55.6	Moderate
Lowhagen, 2002[24]	Yes	No	Yes	Yes	Yes	No	Yes	No	No	66.7	Moderate
Bessa, 2004[25]	No	Yes	Yes	Yes	Yes	Questionable	Yes	No	Yes	55.6	Moderate
Dos Santos, 2004[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	66.7	Moderate
Shulman, 2004[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	77.8	Low
Lorette, 2006[28]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	66.7	Moderate
Parlak, 2006[29]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Questionable	66.7	Moderate
Parks, 2007[30]	Yes	No	Yes	Yes	Yes	Questionable	Yes	No	Yes	66.7	Moderate
Majorana, 2010[31]	Yes	Questionable	Yes	Yes	Yes	Yes	Yes	No	No	66.7	Moderate
Sawair, 2010[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Questionable	55.6	Moderate
Celik, 2013[33]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Questionable	55.6	Moderate
Barrientos Sanchez, 2014[34]	Yes	Questionable	Yes	Yes	Yes	No	Yes	No	Questionable	55.6	Moderate
Perrotta, 2020[35]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	55.6	Moderate

Yes | No | Questionable

Q1: Was the sample frame appropriate to address the target population? Q2: Were study participants sampled in an appropriate way? Q3: Was the sample size adequate? Q4: Were the study subjects and the setting described in detail? Q5: Was the data analysis conducted with sufficient coverage of the identified sample? Q6: Were valid methods used for the identification of the condition? Q7: Was the condition measured in a standard, reliable way for all participants? Q8: Was there appropriate statistical analysis? Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately? RoB: Risk of bias

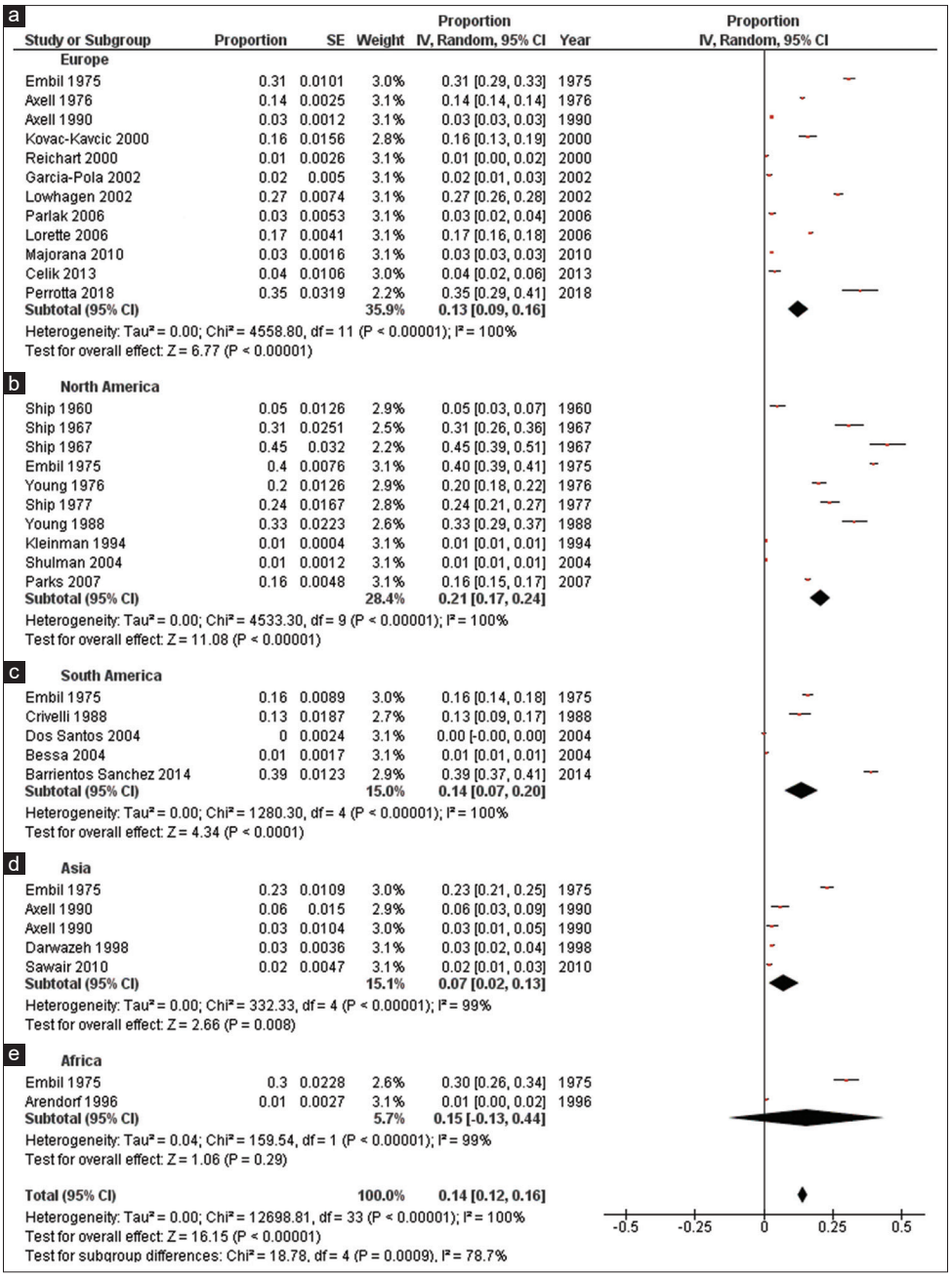

Figure 2: Study data and forest plot graph for the pooled prevalence of recurrent herpes labialis worldwide and in different continents: Europe (a), North America (b), South America (c), Asia (d), and Africa (e)

regarding HSV infection, inadequate information concerning preventable triggers, and an absence of the implementation of suitable treatment regimens.[33] In North America, the seroprevalence of HSV-1 ranges from 57% to 80% among adults. Conversely, in Asia, these seroprevalence rates are notably high (75%) in the adult population, particularly among those of low socioeconomic status, and lower (50%) in the pediatric population, attributable to epidemiological shifts that demonstrate a decline in HSV-1 seroprevalence in younger age groups. The mean incidence of RHL is approximately 1.6 per 1000 patients per year, with a prevalence of 2.5 per 1000 patients. However, these figures vary considerably between countries and different communities, including a higher prevalence in women.[36]

In the present study, the pooled prevalence of RHL in the child population was 3%. Of the six studies that examined this variable, three[18,23,25] reported slightly lower prevalences (≤2%), and one[14] found a higher prevalence (13%). In the adult population, the pooled RHL prevalence was 17%. Of the 22 studies that focused on adults, 12 of them,[8,10,12,16,17,19,20,22,26,27,32,33] reported much lower percentages (≤6%), while other six,[9,10,15,24,34,35] communicated much higher percentages (≥27%).

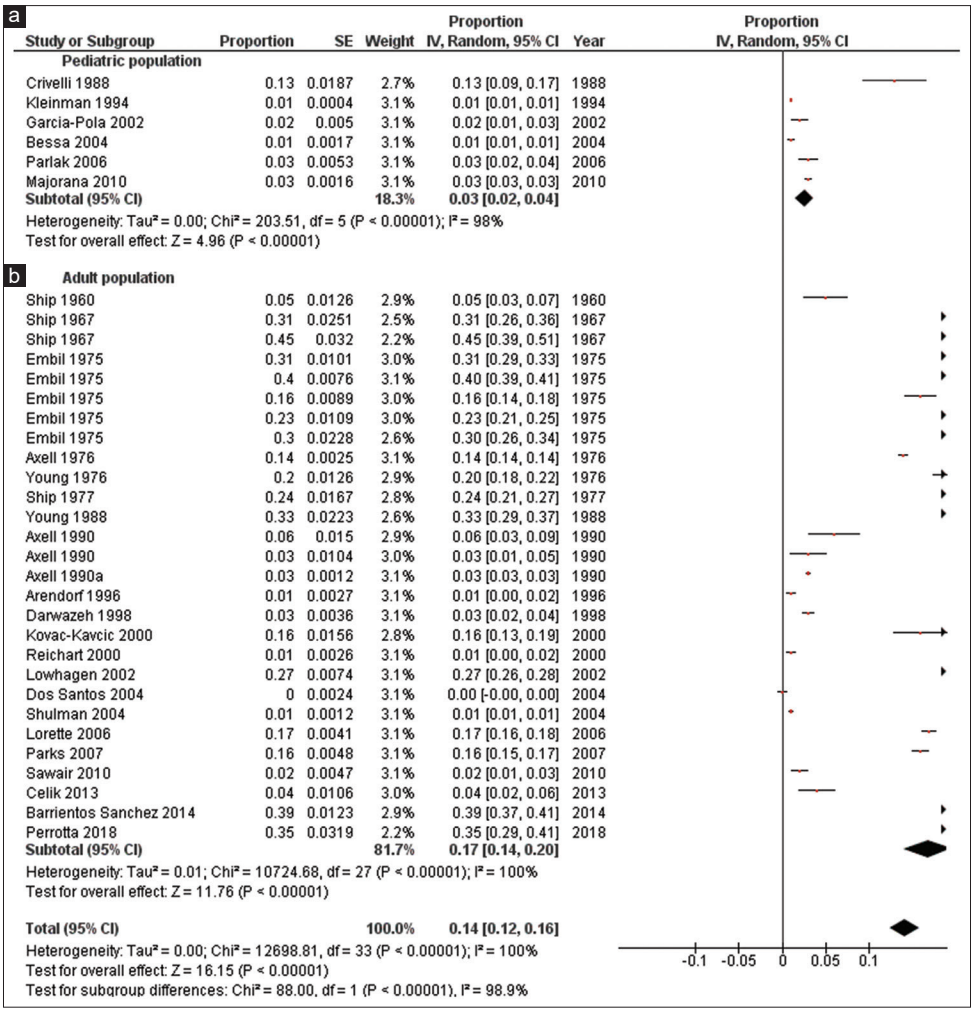

Figure 3: Study data and forest plot graph for the pooled prevalence of recurrent herpes labialis in pediatric (a) and adult (b) populations

The prevalence of RHL is associated with cumulative HSV infection, with adults exhibiting a higher prevalence compared to children. Furthermore, the prevalence of RHL is higher in individuals residing in larger cities (with populations exceeding 1 million) compared to those inhabiting smaller cities. A correlation has been identified between poverty levels and RHL prevalence.[37] Individuals with low incomes exhibited higher RHL prevalence and HSV seropositivity compared to those with middle or high incomes.[38] The ethnic influence on RHL is also notable, with a higher prevalence observed among non-Hispanic whites compared to non-Hispanic blacks.[39] Furthermore, the seroprevalence of HSV increases with age. This phenomenon may be attributable to generational disparities in awareness, perception, and education regarding herpetic infections, or alternatively, to the declining prevalence of herpetic manifestations with advancing age, which could introduce a recall bias in older subjects.[40]

The present study is not without its limitations. Primarily, the absence of studies in certain geographical regions of the world hinders precise evaluation of the results. Secondly, the high heterogeneity observed in some comparisons necessitates a cautious interpretation of the results. Thirdly, discrepancies between studies may be attributable to the analytical approach employed or to the characteristics of the study populations. Finally, further studies are needed to determine the prevalence of RHL in larger and more geographically diverse populations around the world.

Conclusions

In this meta-analysis, the pooled prevalence of RHL worldwide was 14%, with 3% observed in the pediatric population and 17% in the adult population. Looking at the different continents, the highest prevalence of RHL was observed in North America (21%), followed by Africa (15%), South America (14%), Europe (13%), and finally Asia (7%).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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