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Long Term Effects of Soft Contact Lenses on Corneal Endothelium: A Systematic Review and Meta-Analysis

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Abstract

Objective

To evaluate the effects of long term use of soft contact lenses on corneal endothelium.

Methods

The literature search was conducted through PubMed, Embase, and Cochrane databases up to March 2025. Studies assessing corneal endothelial parameters in long-term SCL users (> 6 months) compared to non-wearers were included. Data were extracted on the Endothelial Cell Density (ECD), Endothelial Coefficient of Variance (ECV), Percentage of Hexagonal Cells (HEX), Central Corneal Thickness (CCT), Corneal Fluorescein Concentration (CFC), and the Endothelial Cell Permeability (ECP). Publication bias was examined through a funnel plot and further investigated by a sensitivity analysis. Data was analyzed with Classical Statistics using Jeffrey's Amazing Statistical Package (JASP).

Results

A total of 190 cases and 254 controls were involved in the 6 studies that achieved pooled effect sizes, with 95 percent confidence intervals (CIs) and P-value of various corneal endothelial parameters and referred to as follows: ECV, 0.943 [0.077 to 1.810, (0.039)]; ECD, 0.712 [-0.095 to 1.519, (0.070)]; HXG, 0.800 [−0.038 to 1.637, (0.056)]; CCT, 0.196 [−0.956 to 1.348, (0. 275)]; CFC, 0.374 [−3.342 to 4.089, (0.423)]; and ECP, 0.901 [−5.796 to 7.597, (0.377)]. The values of the heterogeneity (I^2%) expressed moderate to high heterogeneity in ECV (79.5), ECD (76.9), HEX (75.5), and ECP (84.0). Conversely, there was low heterogeneity with CFC (I^2= 51.0) and CCT less than 25%. No major publication bias was identified through residual funnel plot analysis.

Conclusion

The long term use of the soft contact lenses has a significant impact on ECV.

Introduction

Soft contact lenses (SCLs) type of vision correction is a well-recognized and quite popular kind of contact lens that provides more initial comfort and cosmetic acceptability compared to glasses and other rigid lenses. According to the recent estimates, there are more than 140 million people around the world wearing contact lenses, and most wear soft contact lenses [1].

The use of SCL's over the short-term is reasonably safe, however, there have been concerns cited regarding the long-term effects of the wearing of SCLs on the ocular surface and the cornea in general.

SCL's encompasses both hydrogel and silicone hydrogel lenses, but that their material differences may influence endothelial outcomes. The factors that may occur as a result of prolonged use of SCLs include a decrease in oxygen transmission and tear film instability that can cause alterations of the corneal epithelium, limbal hyperemia, and dysfunction of the meibomian glands [2, 3]. Also, it has been shown that chronic lens wear is associated with changes in the corneal endothelial cell morphology, which are the increase in cells variability and hexagonality reduction. Even though, the currently available lenses (Silicon hydrogel) are more permeable to oxygen, and thus some of these risks are eliminated, there is still the need to conduct long-term follow-ups to make sure that the ocular surface is intact and will not develop other complications [4].

The endothelium is important to fluid homeostasis in the cornea by the pump leak mechanism and it has a small capacity to regenerate [5]. Therefore, the contact lenses can cause structural or functional undermining through hypoxic stress induced by the lens [6, 7]. Endothelial cell density (ECD), endothelial cell coefficient of variation (ECV), hexagonality (HEX) central corneal thickness (CCT), endothelial cell permeability (ECP) and corneal fluorescein concentration 6 hour after topical application (CFC) are parameters commonly used to evaluate the health of the endothelium [8, 9, 10].

There are various studies examining these parameters on SCL users but the results do not agree. Others have noticed considerable endothelial changes with wear/ long-term wear or lenses of low oxygen permeability [11–13], others have noticed no or reversible changes with newer high-Dk optical lenses and appropriate lens hygiene [14, 15]. Long-term wearers have been specifically observed to have a decrease in ECD and an increased polymegathism (increased ECV) [16–18]. Also, reduced hexagonality which is the reflection of a change in cellular morphology has also been reported [19].

Another key parameter is CCT since it is the indirect measurement of pump endothelial functioning. Although there are records of studies that have shown minimal changes in CCT among lens wearers [20], others present that it thickens with time due to hypoxic constraint [21]. The development of advanced imaging modalities like specular and confocal microscopes assists in imaging sub-clinical changes in ECP by offering greater understanding of the cellular metabolic activity and permeability in long-standing lens users, which were no detected by routine slit-lamp biomicroscopy.[22].

Methods

The meta-analysis and systematic review were done using the PRISMA 2020 checklist [23] entailing the systematic reviews and reporting of meta-analyses. The protocol has been recorded in the PROSPERO database with the registration number as in the following: CRD42024608492.

Search methodology

An extensive literature search was carried out to find out the implications of soft contact lenses on corneal endothelium in individuals more than 18 years old. The research question was informed with the help of the PICO framework and states: Does the prolonged use of soft contact lenses over a period of

more than six months impair the endothelium of the cornea in comparison to its non-wearers? Here, **Population** involved all people who had been using soft contact lenses over a period of more than 6 months; the **Intervention** involved usage of soft contact lens; the **Comparison** involved non-wearers; and the **Outcome** was any variation in corneal endothelial dynamics. According to this PICO formulation, a focusing search strategy was undertaken on PubMed, Embase and Cochrane databases. Besides, the reference lists of the chosen studies have been manually searched to find possible relevant articles that have not been identified based on the initial database search.

Eligibility criteria and study selection

The following parameters were included to allow selection of articles to be used in the study.

1. Comparative Cross-Sectional studies.
2. Research was done by subjects who wore soft lenses over a period of 6 months or longer aged above 18 years.
3. Studies that included subjects using soft contact lenses for more than 6 months aged above 18 years.

Exclusion Criteria

The review were the studies that fulfilled any of the subsequent criteria:

1. Animal-based research
2. In vitro(laboratory-based) studies
3. Quasi-experimental designs
4. Case reports and case series
5. Articles published in language other than English.

The screening process automatically eliminated duplications records.

Data extraction

A team of researchers used an Excel spreadsheet to extract data from the included studies based on predefined criteria, including sample size, study design, and geographic location. Team member A and team member B extract data from in the excel sheet for the individuals wore soft contact lenses for at least one year or above.

Corneal endothelium parameters like ECD, ECV, HXG, CCT, ECP and CFC for the both group along with numbers included in the Excel spread sheet so that it could be confirmed for the meta-analysis using JASP Software.[24]

Risk of bias assessments for eligible studies

The risk of bias of the examined studies was estimated with a help of one of the scales, namely, Newcastle-Ottawa Scale (NOS). The tool is highly aimed at assessing the quality of the non-randomized studies in systematic review and meta-analysis [25]. The NOS is an eight-item measure that awards zero to nine stars where studies with a score of 7 or more are deemed to be of good quality and a score of less than 7 is of poorer quality.

It has three important primary domains of evaluation which are assessed by the NOS:

- Selection (One to four stars)
- Comparability (0 to 2 stars)
- Outcome/Exposure (1–3 stars/local)

The value of the points is assigned according to the criteria, which are pre-determined and categorized as follows:

- **Good quality**: 3–4 stars in the Selection domain AND 1 2 stars in Comparability AND 2–3 stars in Outcome /Exposure
- **Fair quality**: 2 stars in Selection AND 1–2 stars in Comparability AND 2–3 stars in Outcome/Exposure
- **Poor quality**: 0–1 star in Selection OR 0 star in Comparability OR 0–1 stars in Outcome /exposure

See Table 1, for a breakdown in detail.

Data analysis

To conduct data analysis, means and standard deviations (SDs) were computed to report baseline value of continuous variables (see Table 2), and frequencies and percentages were stated to analyze categorical data. Where unavailable, standard deviations are then calculated using the confidence interval (CI) width and sample size as: SD =CI_Width / (2 x 1.96) × √(Sample Size), using Microsoft excel (version 16). The value of effect was obtained by employing the formula of Cohen D in an online calculator. In t-tests, the calculations of effect size were inserted into the calculator using the value of the means, SD and sample size of both intervention and control groups from Excel sheet. A formula was also used in excel to calculate standard error of effect size.

$$\text{Standard error (SEg)} = \sqrt{\frac{n_1 + n_2}{n_1 \times n_2} + \frac{d^2}{2(n_1 + n_2)}}$$

The Excel spreadsheet contained a specific column where the effect size along with its error was to be entered in order to have a list of the effect size and its error per study. These values and the accompanying labels of studies were subsequently exported to the Jeffrey's Amazing Statistical package (JASP) with a view of performing the meta-analysis. This included the generation of forest plots, funnel plots, and the calculation of the pooled effect size. A fixed-effects model was applied for Central Corneal Thickness (CCT), while random-effects models were used for analyzing the remaining parameters.

Results

Literature search results

A comprehensive search of all selected databases initially identified 42 studies. After the removal of duplicates, 12 studies remained for full-text screening. Following the application of the predefined inclusion and exclusion criteria, 6 studies were considered eligible and included in the final analysis. Notably, four of the included studies were published before 2000, in which the soft contact lenses (SCLs) were made of hydrogel material, whereas two studies were published after 2000, where the lenses were composed of silicone hydrogel material. In the PRISMA flow diagram (see Fig. 1), the achievement of the selection process of studies is shown.

Features of the included studies

There were 6 comparative cross-sectional studies chosen that involved a total of 444 individuals divided into soft contact lens (SCL) group (190 individuals) and control group (254 individuals). The design of all of the chosen studies was a comparative cross-sectional design. Totals of the six major parameters are presented in Fig. 1 as endothelial cell coefficient of variation (ECV), endothelial cell density (ECD), percentage of hexagonal cells (HEX), central corneal thickness (CCT) and endothelial cell permeability (ECP) and corneal fluorescein concentration (CFC) six hours following topical administration. A description of baselines of the characteristics of studies have been reported in Table 2. The participants were aged above 18 years, experimental group included long-term SCL wearers and the remaining were non-SCL users who formed the control group.

Quality assessments

Based on the statistical analysis, there is the comparison of ECV, ECD, HEX, CCT, ECP and CFC groups, with the most important statistical measures of mean change and SD.

Statistical analysis

The commonly used statistical indicators in the available literature include mean change and standard deviation (SD). The comparison of the crucial six parameters including ECV, ECD, HEX, CCT, ECP, and CFC is a good way to compare outcomes in a comprehensive manner.

Endothelial Cell Coefficient of Variance (ECV)

The results of the meta-analysis enclosed five studies comparing the effect size of the endothelial coefficient of variation with an estimated mean difference of 0.943 (p = 0.039), which depicted the statistically significant difference between the soft contact lens wearers and the controls. The confidence interval ranged between 0.077 and 1.810 which is an additional evidence of inconclusiveness of the findings. (Table 3). This parameter also showed a moderately high level of heterogeneity according to the I^2 value of 79.451 percent and the significant outcome of the Q-test ($p < 0.001$) and hence the effects of soft contact lenses on ECV% may not be easily interpreted, as the level of difference in results among the studies is high. (Table 4)

Endothelial Cell Density (ECD)

The results of the meta-analysis included 5 studies that assessed the effectiveness of densities of endothelial cells among people wearing soft contact lenses and those in controls groups which is estimated to be an average of mean difference of 0.712 ($p = 0.070$) that was not considered to have significant differences. The finding was the confidence interval was between − 0.095 and 1.519 implying that there was uncertainty on the direction of effect (Table 3). The level of heterogeneity was moderate ($I^2 = 76.8942\%$), and this shows that there was a big diversity in studies. The Q-test was significant ($p < 0.001$), which made inferences to the involvement of the study-specifics in the outcomes. (Table 4)

Endothelial Cell Hexagonality (HEX)

The meta analysis of four studies assessed the effect size of endothelial hexagonality and revealed an estimated mean difference of 0.800 ($p = 0.056$) which again establishes that there was no significant result between soft contact lens group and control groups. The confidence interval is -0.038 to 1.637 which means the effect is uncertain; to a great degree. The heterogeneity level is moderate ($I^2 = 75.481\%$) and non-significant Q-test ($p = 0.008$) shows that there was no significant difference in the results of the studies, suggesting the mindfulness of determining the role of soft contact lens wear in endothelial hexagonality. Although there is the likelihood of the negative trend, variability indicates that characteristics of individual studies might be important determinants of such results. (Table 4)

Central Corneal Thickness (CCT)

In the meta-analysis, the data of two studies were included that measured the effect sizes of central corneal thickness, simulations indicated that the estimated mean difference between soft contact lens wearers and controls was 0.196 ($p = 0.275$) which also showed no significant difference between the two conditions. The confidence level CHI was between − 0.956 and 1.348 which further logistically was the indecisiveness of any results. (Table 3). Due to extremely high heterogeneity, fixed effect model was applicable. The results of the Q-test indicated no important heterogeneity ($p = 0.645$), indicating the role of characteristics specific to studies in the results.

Corneal Fluorescein Concentration (CFC)

The meta-analysis involved two studies that compared the effectiveness of the corneal concentration of fluorescein between individuals who wear soft contact lenses and the control groups at an estimated p

value of 0.423 showing no significant amount. The confidence interval was between − 3.342 and 4.089 (Table 3) implying doubt with regards to the direction of the effect. Low heterogeneity was noted (I^2 = 51.035%) and this indicates high degree of variability across research studies. Statistically, the indication of the results of the Q-test (p = 0.153) indicated the lack of significant heterogeneity suggesting the role of study specifics. (Table 4)

Endothelial Cell Permeability (ECP)

Two studies included in the meta-analysis assessed the extent of the endothelial cell permeability of participants wearing soft contact lenses and participants in control groups that gave an estimated mean difference of 0.685 (p = 0.337) showing an insignificant statistically different value between two studies with endothelial cell permeability. The effects direction was not confident because the confidence interval was between − 5.796 and 7.597 (Table 3). An intermediate level of heterogeneity (I^2 = 84.034%) was observed that suggests high degrees of inconsistencies across the studies. The Q-test outcomes declared that there is no noteworthy homogeneity (p = 0.012) see Table 4.

Model Fit Statistics and Information Criteria for Endothelial Cell Densities, Coefficient of Variation, Hexagonality, Central Corneal Thickness, Corneal fluorescein Concentration and Endothelial Cell Permeability using Maximum-Likelihood and Restricted Maximum-Likelihood Estimation is represented in Table 5.

Discussion

The objective of the systematic review and meta-analysis was to find out whether there is a significant long-term effect of SCL's (both hydrogel and silicon hydrogel) wear on corneal endothelium. The statistical finding showed the statistically significant effect on the endothelium coefficient of variation (ECV) which showed the possible morphological development of endothelium cells with long duration of lens wear. The publication bias was also determined with the funnel plot that depicted no significant bias. Since it applies classical statistics, a random-effects model was employed on all parameters except the central corneal thickness (CCT), with which a fixed-effects model was employed. The possibility of bias in the enrolled studies was assessed with the Newcastle-Ottawa Scale (NOS), and the outcomes showed that the risk of bias was low in studies.

Out of the six endothelial parameters investigated, endothelial cell coefficient of variation (ECV), was the only statistically significant change indicating that prolonged use of SCLs might have consequences on endothelial cell morphology. Such a parameter indicates pleomorphism or size variability of cells and its rising point to a stressed endothelium [32]. These results are consistent with prior reports demonstrating that endothelial cell remodeling and morphologic instability could be caused by the long-term hypoxic stress, which is induced by SCLs [33].

Endothelial cell density (ECD) and hexagonality (HEX) had positive effect sizes that were not significant. Nonetheless, any trend and possibility of clinical significance seems to be present as the borderline p-value is 0.070 between ECD and HEX (0.056). Earlier researchers have described gradual decreasing of ECD over an extended duration of using SCL particularly when the lenses have low oxygen-permeability [34, 35]. Similarly, diminished hexagonal cells, a signifier of cellular pleomorphism, have also been reported among long term wearers [36].

Remarkably, there are no significant changes in the thickness of the central cornea (CCT) and corneal fluorescein concentration (CFC) so that, perhaps, the corneal edema or intraocular permeability may not have much effect in the long term of modern SCLs. These results agree with the emergence of high oxygen-transmissible materials (e.g. silicone hydrogels), that have alleviated complications of corneal hypoxia [37].

Nonetheless, the permeability of endothelial cells (ECP) was not significantly different, yet it was widely uneven (I^2 = 84 percent), which could be explained by differences in research methods as well as by diversity in the study population and lens type. This emphasizes the need to set up uniform measures which can be adopted in subsequent studies.

Moderate to high heterogeneity of ECV, ECD, HEX, and ECP demonstrate the differences in the quality of the study, lens materials, wear duration, and imaging methods (example, specular, and confocal microscopy). In spite of those flaws, the publication bias is absent, which harbors the assumption that our averaged estimates are sound.

Our findings strengthen the idea that chronic use of SCL also affects the corneal endothelial morphometry with measurable results, mainly in elevated ECV. New changes might not be clinically important in healthy persons but they might be relevant to other patients whose endothelial functions are at the border such as in patients with ocular morbidities, preoperative assessments before intraocular surgical procedures and so on [38]. Longitudinal analysis is also required to evaluate progression and reversibility of the change, particularly with types of lenses and lens wear prescription regimens. Future research should specifically compare hydrogel and silicone hydrogel lenses to determine whether modern materials mitigate endothelial changes. Limitations includes the predominance of pre-2000 studies constrains the applicability of our findings to modern silicone hydrogel lenses, which have been widely available for nearly three decades. We have emphasized that future systematic reviews and meta-analyses should focus on contemporary lens materials and designs to better understand their long-term impact on the corneal endothelium. Also emphasis should be done regarding methodological differences are a likely source of variability and should be standardized in future research to improve reliability and comparability of outcomes.

Conclusion

Long-term use of SCL's significantly effects one of the corneal endothelial parameters which is endothelial coefficient of variance. To better understand how long-term use of soft contact lenses affects the corneal endothelium, especially the increase in endothelial cell variation, future studies should be well-designed, long-term, and use advanced imaging tools. It's important to compare different types of contact lens materials and wearing schedules to see how they influence endothelial health. Research should also explore whether these changes are reversible (rebound effect) and if they have any long-term effects on vision or eye health. Finally, using consistent methods and reporting standards across studies will help produce more reliable and comparable results.

Declarations

Conflict of Interest:

There is no conflict of interest in this manuscript.

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There are no sources of funding for this manuscript.

Author Contribution

Mehmona Asgher: data extraction, data analysis, wrote main manuscriptSaif Ullah: Critical analysis, reviewed manuscript, data extractionMutahir Shah: data extraction, reviewed manuscript

Data Availability

I used data extracted from published original studies and have appropriately cited all sources in the manuscript. The original articles are publicly accessible, allowing verification of the data used. In addition, an Excel file containing the extracted dataset from the included studies will be provided as a supplementary file for transparency and reproducibility.

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Tables

Table 1: Newcastle-Ottawa Scale (NOS) Quality Assessment Scores for Included Studies

Study label	Selection	Comparability	Exposure	ONS Score out of 9
Ali et al., 2021 (Malaysia) [26]	****	*	*	**6**
Chang et al., 2000 (Taiwan) [27]	****	*	**	**7**
MacRae et al., 1986 (New York) [28]	****	*	**	**7**
Lee at al., 2000 (Korea) [29]	****	*	*	**6**
Carlson et al., 1988 (USA) [30]	****		*	**5**
Ahmad et al., 2018 (Malaysia) [31]	***	*	**	**6**

Table 2: Baseline Characteristics: Descriptive Statistics for Age and Soft Contact Lens Wear Duration in Wearers and Controls (Non-wearers)

Study label	Age in years		Duration of CL wear in years	
Author, year, country	**Soft Contact Lens wearer (N) Mean±SD**	**Controls Non-wearers (N) Mean±SD**	**Soft Contact Lens wearer Mean±SD**	**Controls Non-wearers Mean±SD**
Ali et al, 2021 (Malysia) [26]	(72) 22.3±1.97	(24) 21.83±1.34	4.5±2.07	N/A
Chang et al, 2000 (Taiwan) [27]	(34) 23.8±4.2	(116) 23.6±2.9	3.3±1.1	N/A
MacRae et al., 1986 (New York) [28]	(20) 28.0±1.4	(20) 28.3±1.4	6.3±0.76	N/A
Lee et al, Sep 2000 (Korea) [29]	(30) 26.4±6.3	(30) 25.1±7.1	3.3±1.1	N/A
Carlson et al., 1988 (USA) [30]	(10) 26.3±5.2	(40) 29.1±11	N/A	N/A
Ahmad et al, 2018 (Malysia) [31]	(24) 21.46±0.83	(24) 21.04±1.63	N/A	N/A

Table 3: Model Estimation of the Impact of Soft Contact Lenses on Corneal Endothelial Cell Densities, Coefficient of Variation, Hexagonality, Central Corneal Thickness, Corneal Fluorescein Concentration and Endothelial Cells Permeability.

Intercept	Estimate	SE	CI Lower Bound to CI Upper Bound	t	P
*ECV%	0.943	0.312	0.077 to 1.810	3.023	0.039*
*ECD	0.712	0.291	-0.095 to 1.519	2.451	0.070
*HXG %	0.800	0.263	-0.038 to 1.637	3.039	0.056
**CCT	0.196	0.091	-0.956 to 1.348	2.166	0.275
*CFC	0.374	0.292	-3.342 to 4.089	1.278	0.423
*ECP	0.901	0.527	-5.796 to 7.597	1.709	0.337

*Random Effect Model **Fixed Effect Model

ECD(Endothelial Cells Densities),ECV(Endothelial Coefficient of variation),HXG (Endothelial Cell Hexagonality), CCT (Central Corneal Thickness), CFC (Corneal Fluoresceine Concentration 6 hour after topical application) , SE(Standard Error), ECP (Endothelial Cells Permeability), CI(Confidence Intervals)

Table 4: Heterogeneity Statistics for Random-Effects Model Evaluating Endothelial Cell Densities, Coefficient of Variation, Hexagonality, Corneal fluorescein Concentration and Endothelial CellPermeability.

Parameters	Tau	Tau²	SE	I² (%)	H²	df	Q	p
ECV	0.550	0.303	0.312	79.451	4.866	4	19.465	< .001
ECD	0.494	0.244	0.291	76.894	4.328	4	19.876	<.001
HEX	0.453	0.205	0.263	75.481	4.079	3	11.879	0 .008
CFC	0.302	0.091	0.292	51.035	2.042	1	2.042	0.153
ECP	0.685	0.469	0.527	84.034	6.263	1	6.263	0.012
CCT	Nil	Nil	0.091	<25	Nil	1	0.212	0.645

ECV (Endothelial Coefficient of variation), ECD (Endothelial Cells Densities), HXG (Endothelial Cell Hexagonality), CFC (Corneal Fluorescein Concentration, ECP (Endothelial CellPermeability), CCT (Central Corneal Thickness, SE (Standard Error)

Table 5: Model Fit Statistics and Information Criteria for Endothelial Cell Densities, Coefficient of Variation, Hexagonality, Central Corneal Thickness, Corneal fluorescein Concentration and Endothelial CellPermeability. Using Maximum-Likelihood and Restricted Maximum-Likelihood Estimation

	log-likelihood	Deviance	AIC	BIC	AICc
Model Fit Statistics and Information Criteria Endothelial Cell Densities (ECD)					
Maximum-Likelihood	-4.398	12.420	12.796	12.015	18.796
Restricted Maximum-Likelihood	-4.040	8.081	12.081	10.853	24.081
Model Fit Statistics and Information Criteria Endothelial Coefficient of Variance (ECV)					
Maximum-Likelihood	-4.758	12.753	13.515	12.734	19.515
Restricted Maximum-Likelihood	-4.308	8.615	12.615	11.388	24.615
Model Fit Statistics and Information Criteria Corneal Endothelial Hexagonality (HEX)					
Maximum-Likelihood	-2.605	8.658	9.211	7.983	21.211
Restricted Maximum-Likelihood	-2.334	4.669	8.669	6.866	20.669
Model Fit Statistics and Information Criteria Central Corneal Thickness (CCT)					
Maximum-Likelihood	0.530	0.212	0.939	-0.368	4.939
Restricted Maximum-Likelihood	0.171	-0.342	1.658	-0.342	5.658
Model Fit Statistics and Information Criteria Corneal Flourescein Concentration (CFC)					
Maximum-Likelihood	-0.594	2.585	5.189	2.575	17.189
Restricted Maximum-Likelihood	-0.558	1.117	5.117	1.117	17.117
Model Fit Statistics and Information Criteria Endothelial Cell Permeability (ECP)					
Maximum-Likelihood	-1.752	4.867	7.505	4.891	19.505
Restricted Maximum-Likelihood	-1.127	2.255	6.255	2.255	18.255

Figures

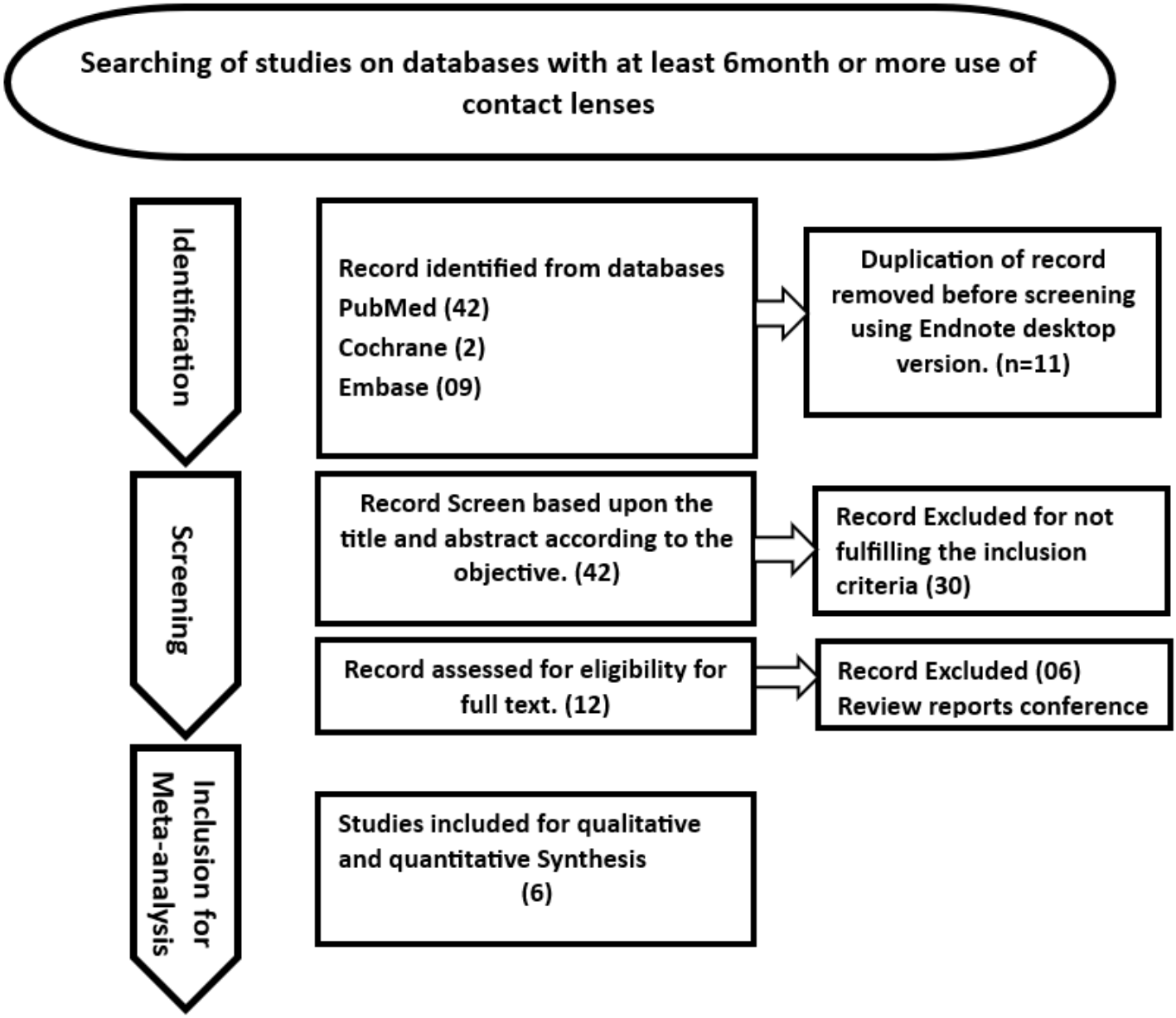


Figure 1

The PRISMA flowchart illustrates the study selection process, detailing the search strategy and the number of studies ultimately included in the meta-analysis