The Effectiveness of Corticosteroids on Eczema: A Comprehensive Meta Analysis

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Abstract

This research delves into the statistical process of meta-analysis, a technique that combines the results of several related randomised controlled trial studies, with the aims of providing a comprehensive review of the effectiveness of corticosteroid creams on the skin condition eczema. This report uses data collected from PubMed (National Library of Medicine, 2024) and the Cochrane Library (2016), where studies are individually selected following specific inclusion and exclusion criteria to ensure they are similar enough to be compiled for meta-analysis. 15 Studies were found to include the comparable dependent variables over one of two measures. A binary measure relating to the number of participants who experience a flare following application of the corticosteroid, or a continuous measure relating to the change in disease severity as assessed by specific numerical scales. Meta-analysis was then performed to determine an overall effect that explains whether there is a statistically significant relationship between applying corticosteroids and reducing the severity of the symptoms of eczema.

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Introduction

What is Eczema?

Eczema is the umbrella classification for seven different inflammatory skin conditions: atopic dermatitis, contact dermatitis, dyshidrotic eczema, neurodermatitis, nummular eczema, seborrheic dermatitis, and stasis dermatitis (National Eczema Association, 2013). Atopic Dermatitis is the most common form of eczema (NHS, 2019) and will be the focus of my analysis. It is derived from atopic meaning a hypersensitive allergy resulting in a reaction affecting the skin, and dermatitis, meaning irritation and rashes caused by genetics, the immune system, infection, and allergies. Atopic Dermatitis is a condition with symptoms including itching, dryness, cracking, soreness, inflammation, weeping and bleeding of the skin. But the social and mental aspects of the condition can affect its sufferers more deeply in forms such as embarrassment and shame. The itching and pain can lead to insomnia which can affect academic and employment performance and punctuality. The National Library of Medicine (2018) defines the itch-scratch cycle as the process that perpetuates the condition. This is where the skin becomes itchy, leading to scratching which compromises the skin barrier allowing irritants to inflame the skin causing itching again. Any attempts to reduce the immediate pain by scratching only makes it worse.

Eczema is currently a condition that has no cure (NHS, 2019) but can be treated for to ease the severity of its symptoms. Moisturisers can be applied regularly to stop the skin from drying out by hydrating the upper layers of the skin which helps to reduce itchiness. Corticosteroids for eczema are anti-inflammatory creams that aim to reduce inflammation and itching and come in a range of strengths prescribed to match the conditions severity. (CKS, 2022) However, it is recommended that taking specific lifestyle choices can help reduce the frequency of flare ups such as selecting loose-fitting softer fabric clothes, keeping a constant temperature within homes, using a dehumidifier, and using non-fragranced soaps and detergents (NHS, 2019). However, newer research according to Medical News Today (2022) suggests that there is a link between eczema and gut health. A controlled diet and consuming probiotics can help reduce the number of harmful bacteria, in turn, reducing the effects of a leaky gut.

The severity of eczema can be numerically identified on several different scales. Three very common measures are EASI, SCORAD, and POEM. EASI (Eczema Area and Severity Index) is a scoring tool that can measure the extent of eczema across the body and its severity (Oakley 2015). Within this, the body is split into sections: the head and neck, the trunk including genitals, the arms, and legs including buttocks. Then, these areas are quantified from 0% to 100% on how present eczema is. Then, each section of the body is ranked by how intense certain symptoms are, being redness, swelling, scratching, and lichenification (thickening of skin) (Oakley 2015) from 0 to 3. The second scale is SCORAD (SCORing Atopic Dermatitis). In this, the body is split into sections differently and instead uses 'the rule of 9' (Oakley 2009) identified as the head, neck, both arms, both legs, front trunk, back, and genitals. However, are brought together to determine the total area of body affected as a percentage. Then, the intensity of symptoms is ranked from 0 to 3, but this time, includes redness, swelling, oozing, scratch marks, lichenification, and dryness. However, uniquely considers subjective factors such as sleeplessness. The last measure, POEM (Patient Oriented Eczema Measure), is a method that allows the patient to complete a questionnaire that self-quantifies the duration of their symptoms (The University of Nottingham, n.d.) resulting in a score from 0 to 28.

Each method has their own strengths and weaknesses, and it is up to the researcher to decide the most appropriate measure. For example, SCORAD provides quite a comprehensive assessment but requires specialists to identify symptoms. EASI is simpler but does not consider any patient ranked scoring and instead relies solely on the specialists. POEM considers the patient's perspective on their eczema, however, can be at risk to the subjective nature of self-reporting.

Motivation

Eczema is an extremely common condition, and according to the National Eczema Society (2019), atopic dermatitis affects 1 in 5 children and 1 in 10 adults in the UK. But, as someone who has lived with eczema since birth, I have always found that regardless of the routine application of moisturisers, corticosteroids and sticking to strict lifestyles, that symptoms flare up regardless. So, combing this with my existing knowledge of eczema, performing analysis into how effective interventions are at reducing eczema symptoms was fitting.

Overview of Methodology

Hierarchy of evidence

The hierarchy of evidence pyramid is a graphic that helps denote the increasing levels of statistical power in evidence-based research.

Figure 1:Hierarchy of statistical evidence pyramid (Murad et al., 2016)

Case Reports are the smallest of any descriptive study that usually features 3 or less participants allowing for initial presentation of the outcome of a study. Case studies are very similar except that they generally contain more participants (Ganesan, 2022). They often have no approved study design but help support further research in the field.

Case Control Studies and Cohort Studies are considered primary observational studies. Observational studies are used to answer a research question based purely on what the researcher observes (George, 2022). In these studies, there are no control groups, having only observations of subjects to conditions and characteristics they already have. In other words, observing naturally occurring events. Cohort studies follow a select group of participants that share a common characteristic over a long period of time, often many years (Barrett and Noble, 2019). While case control studies observe two groups, one that has participants with the outcome of interest and a second group constructed of participants without the outcome of interest (Tenny, Kerndt and

Hoffman, 2023). An example of a case control study would be analysing the effects of a disease against those without the disease.

Randomised controlled trials are an example of non-observational primary data, meaning that a study is designed to assess the effects of an active treatment by providing it to one group, called the intervention group, while another group, called the control group, is used as a baseline for any comparisons. the data is collected firsthand by a researcher or a team of researchers (Hassan, 2022) and then analysis is performed on their findings to come to statistical conclusions.

Meta-analysis and systematic review are forms of secondary data. This refers to information collected, processed, and published by someone else, rather than the researcher gathering the data firsthand (Hassan, 2022).

Randomised Controlled Trials

The data utilized in meta-analysis is derived from randomised controlled trials (RCTs). Each step to performing a correct RTC are essential to reduce the impact of bias on clinical trials with the end goal of ensuring accurate, repeatable results. Cochrane (2016) determines bias in a randomised controlled trial over several categories: randomisation, allocation concealment, blinding of participants, blinding of data gatherers, blinding of research analysts, incomplete data, selective reporting, and a final category for any other unordinary bias.

Randomisation

Randomisation is the process of allocating study participants into different groups purely by chance, in this case, to either the control group or experimental/intervention group. Methods of randomisation used most in clinical trials include simple, blocked, or stratified. Simple randomisation is the most rudimentary and involves equal chance of being allocated to either group. The benefit of simple randomisation is it's straightforward and transparent nature, particularly when handling large sample sizes, as the likelihood of imbalance gets lower as sample size increases. However, smaller

samples run a high risk of creating uneven groups simply by chance, potentially resulting in groups too small to incur any statistical significance.

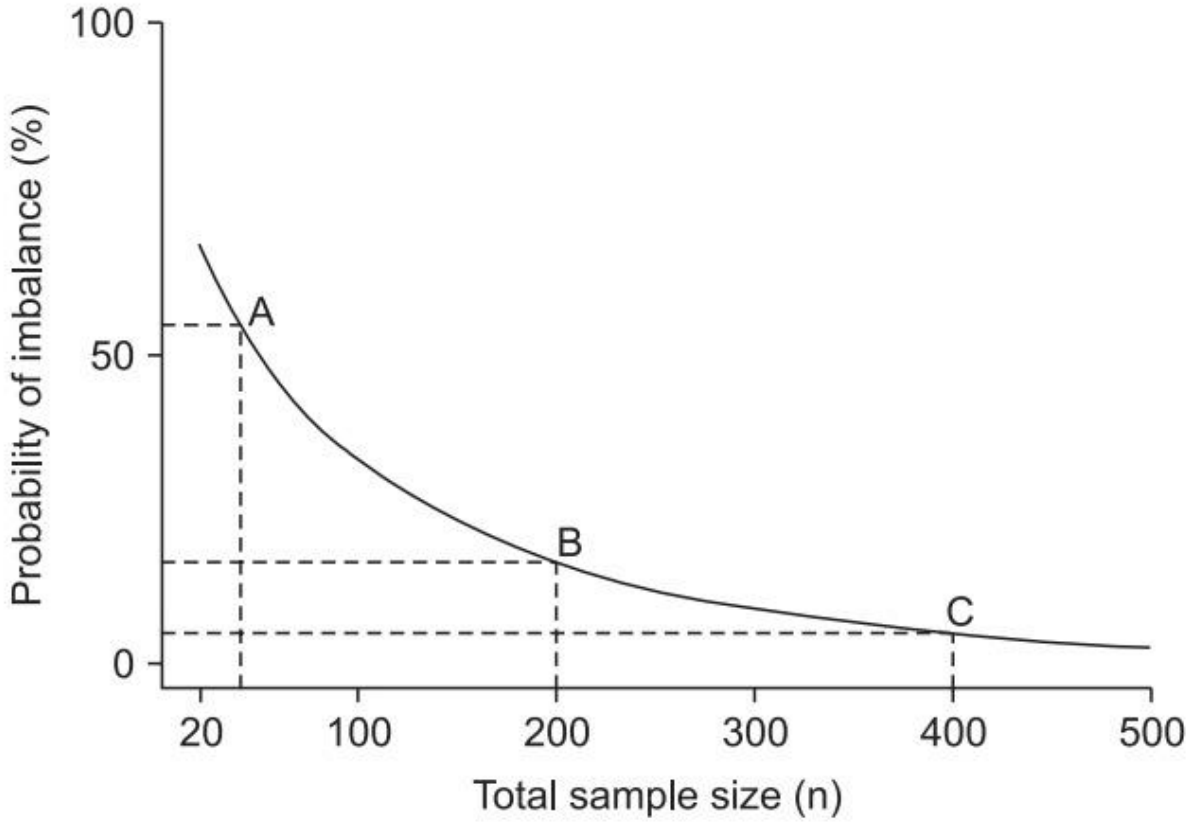

Figure 2:Graph of probability of imbalance against total sample size (Lim and In, 2019)

Using Lim and In (2019) to explain this graph: at point A, when n = 40, there is a 52.7% chance of imbalance beyond 10% of what is expected. At point B, when n = 200, there is a 15.7% chance of imbalance. And at point C, n = 400, there is a 4.6% chance of imbalance. This clearly demonstrates how as sample size increases, the chance of imbalance between the groups decreases. Meaning that simple randomisation is most applicable when handling large sample sizes.

Blocked randomisation is a method that can help researchers deal with small sample sizes by removing the probability of imbalance. This method includes allocating participants into groups or "blocks" of equal size. Using Roberts and Torgerson (1998) to help explain, if a study requires 16 participants, 4 blocks containing 4 individuals would be appropriate. For the 4x4 study, each block could have a predetermined sequence of AABB, ABAB, ABBA, BAAB, BABA or BBAA where A and B represent either experimental or control. To each block, one of the sequences are randomly assigned and

then 4 participants are selected, usually through the order that they appear for the study, and then allocated to a group depending on whether they land on an A or a B. The main benefits and use of blocked randomisation is to allow smaller sample sized research to remove variable group sizes so that smaller treatment effects can be detected. However, forcing equal group sizes potentially harms the unpredictability of treatment assignments (Schulz and Grimes, 2002), which for larger samples can introduce bias. Furthermore, having to implement blocks for large sample sizes takes up research time which is not necessary given the ease of simple randomisation. So, to summarise the use of simple and blocked randomisation, when handling smaller sample sizes, using blocked randomisation would be preferred, and handling larger sample sizes, simple randomisation would be preferred.

Yet, in both simple and blocked randomisation, cofounding variables may exist in the population that are predicted to incite a statistically significant result. Stratified randomisation is a technique that aims to overcome this problem by creating a sample representative of the population. In this method, the participants are divided into homogeneous subpopulations called strata (Thomas, 2020). These strata are most commonly demographic characteristics such as sex, age, or race but in the case of researching eczema, strata could also include severity of the condition or location on the body. Taking age as an example, age could be categorised into 18-25, 26-35, 36-45, 46-55, 56-65, 66+. It is important that each participant can be divided into each stratum exactly once so that the sample is both representative of the whole population but not also an overrepresentation of certain subgroups within the population. Once each participant has been identified, simple or blocked randomisation is used to assign participants to either the intervention or control group ensuring that both groups have a similar distribution of participants for each stratum. By spreading these subgroups evenly across the experimental and control groups, the effect of the cofounding variables is controlled for since they will appear equally in both allowing just the intervention to be analysed.

Bias can be introduced to a randomised controlled trial through randomisation usually in two ways. Either, allocation was made without a random process, or a method not deemed to be appropriate was applied which is why it's important to understand the correct usage of each form of randomisation.

Controlling

The existence of a control group in an RTC is essential in identifying and isolating the effect of an intervention. Control groups aim to replicate the experience of participants undergoing the intervention without providing any treatment effect. This is done by providing participants with a placebo that is indistinguishable from the intervention through look or feel. The reason a placebo is given rather than providing nothing is due to the placebo effect. Seladi-Schulman (2020) helps describes the placebo effect in clinical research. For example, taking a specific pill for to induce pain relief can cause simply taking of the pill to become associated with that relief. Thus, receiving a similar-looking pill with no active treatment may still report pain relief. In eczema research assessing the effect of a corticosteroid, a corticosteroid would be the intervention while a cream of similar feel and substance could be provided as the placebo. This in turn allows researchers to compare the effect between application of the steroid and application of no steroid while controlling for the effects of patient bias. To reduce the impact of the placebo effect, in turn, minimising bias, blinding is employed.

Blinding

Blinding can come in 4 forms, no blinding, single blinding, double blinding, or triple blinding. No blinding refers to research where both the participant and researcher are aware of whether they receive the intervention or the placebo. This method has a high likelihood of introducing conscious or subconscious bias. For example, a participant aware that they are receiving a placebo may alter their normal day-to-day behaviour to provide a result they believe to be desirable. Single blinding is when only the researcher is aware of which participants receive the intervention. While less exposed to conscious bias if researchers are ethical, subconscious bias may result in favouring participants with more severe symptoms or within certain demographics. Double blinding is when neither the researcher or the participant is aware of who receives the intervention or placebo. This ensures that any researcher or participant bias is generalised to both the intervention and control group which maintains study integrity. Triple blinding is where neither participant, researcher, nor data analyst are aware of intervention/control allocation. This is the most rigorous assessment, used when analyst expectations may cause the data to be analysed in many ways until arriving at the expected outcome even if merely by chance (Thomas 2020).

Meta-Analysis

Meta-analysis is a statistical technique employed to synthesize data from multiple related studies focusing on a specific topic (Cochrane, 2016). The minimum number of studies required is therefore two, but increasing the number of studies only increases the statistical power of the meta-analysis. Data is collected from randomised controlled trials and then the findings are combined to perform statistical analysis on. This analysis involves comparing the effect sizes of each study. Simply, this is the difference in the average results of the intervention and control. The effect sizes can then be combined to calculate an overall effect. It is important to note that meta-analysis is not simply merging similar smaller sample studies into one larger sample study (Shorten and Shorten, 2012). In other words, the data gathered and analysed are not from the individual participants of each study but instead from just the results.

Performing a meta-analysis can vary depending on the type of results researchers have but Shorten and Shorten (2012) summarises the steps into 5 universal points:

1) Identify the research question and propose hypotheses,
2) Perform a systematic review to identify studies that are relevant and can be included,
3) Extract data from the included studies along with their sample size and data variability,
4) Calculate the effect sizes of each study and standardise the results,
5) Select an appropriate model to compare the effect sizes across the studies.

As mentioned in the hierarchy of evidence, systematic review is considered its own form of secondary data, yet the process is similar, up to a point, in a meta-analysis. Both present results by combining and analysing data from different studies conducted on similar research topics (Ahn and Kang, 2018). Meta-analysis is employed when the strength of evidence during a systematic review is brought to question, whether it be to determine the existence of an effect, whether the effect is positive or negative, or whether an effect is small or large. Obviously, that means a meta-analysis is not always applicable. For example, if studies are too diverse, the effects of studies found in meta-analysis are meaningless as they have no observable relationship. Additionally, meta-analysis can be quite susceptible to the effects of any bias resulting in incorrectly estimated results (Cochrane 2022). A systematic review that does not use meta-analysis

will present results as a summary of data from the individual studies. It will most likely include statistics relating to the heterogeneity among study results with sensitivity analysis.

Systematic Review

The process of a systematic review is quite extensive and to perform correctly requires the author to adhere to specific rules. The most universal guide can be found at the PRISMA website (2020). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) is an evidence-based minimum set of items for reporting systematic reviews and meta-analyses. PRISMA provides guidelines detailing the process of all methods and results required for a systematic review.

Using the PRISMA (2020) checklist to describe systematic review, firstly, identify the inclusion and exclusion criteria of the meta-analysis. Then, locate all databases, registers, websites, organisations, and reference lists where studies can be found. Search strategies including any keywords or filters should be listed clearly. Once studies are selected that meet the criteria, name them, and explain how they met the criteria.

Note that a systematic review is only as extensive as the available resources and time. Often these are carefully performed by large teams of people with a lot of time and funding that filter through thousands of RTCs. Additionally automatic tools are often employed to aid the researchers in acquiring these RTCs quickly.

Effect Size

When performing a meta-analysis on a binary measure dependent variable, a choice of 4 effect size settings is available: “Log Odds Ratio”, “Peto’s Log Odds Ratio”, “Log Risk Ratio” or “Risk Difference”. All are appropriate measures of effect size but interpreting an outcome as a different effect is a common mistake. For example, misinterpreting the risk ratio as the odds ratio will lead to underestimating the effect of the intervention. The methods for calculating the effect size are as follows:

Log Odds Ratio:

$$Ln\left(\frac{Number\ of\ Success\ (Intervention)}{Number\ of\ Fail\ (Intervention)} \div \frac{Number\ of\ Success\ (Control)}{Number\ of\ Fail\ (Control)}\right)$$

Log Risk Ratio:

$$Ln\left(\frac{Number\ of\ Success\ (Intervention)}{Number\ of\ Participants\ (Intervention)} \div \frac{Number\ of\ Success\ (Control)}{Number\ of\ Participants\ (Control)}\right)$$

Risk Difference:

$$\frac{Number\ of\ Success\ (Intervention)}{Number\ of\ Participants\ (Intervention)} - \frac{Number\ of\ Success\ (Control)}{Number\ of\ Participants\ (Control)}$$

Peto's Log Odds Ratio is more complex and provides a weighted estimate of the standard log odds ratio. This method is most usable when there is believed to be bias because of small event rates. Small event rates are when the Number of successes is small compared to the total sample.

Alternatively, performing a meta-analysis on a continuous measure dependent variable provides 4 different effect size settings. The choice must be made between "Cohen's d", "Hedges' g", "Glass's Delta" or "Unstandardised Mean Difference".

Cohen's d and Hedges' g are the standardised difference between two means and use the same base formula:

$$\frac{\bar{x}_1 - \bar{x}_2}{pooled\ \sigma}$$

However, modification to Hedges' g make it more effective when handling sample sizes of < 20 (Stephanie, 2016) but conversely less effective handling samples any larger. Therefore, choose Hedges' g when studies are small and Cohen's d when samples are large.

Alternatively, there is argument to suggest using Glass's delta which takes only the standard deviation from the control group:

$$\frac{\bar{x}_1 - \bar{x}_2}{control\ \sigma}$$

This is so effect sizes would not differ under equal means and different variance (Stephanie, 2017).

The numerical effect sizes calculated by Cohen's d, Hedges' g and Glass's Delta can give guides into the size of an effect. Of course, given that an effect is statistically significant. These can come in values ranging from 0 to ∞. However, typically values usually range between 0 to 2. Values between 0-0.35 indicate a small effect, between 0.35-0.65 indicate a medium effect, between 0.65-1 indicate a large effect and above 1 indicate a very large effect (McLeod, 2019).

The last measure of effect size, the unstandardised mean difference, is simply the difference in means without considering variance:

$$\bar{x}_1 - \bar{x}_2$$

This method is used when each study in the meta-analysis uses the exact same unit of measurement. For example, ranking the severity of eczema can be done using different scales and while the numerical values will not be the same, can be standardised and the effects can be compared. Yet if, every test uses SCORAD to rank eczema severity, then there is no need to standardise the results.

Random/Fixed Effect Model

Meta-analysis has the option to be modelled using either fixed-effect or random effects to combine the results of studies. Sometimes, selecting either model will present similar results. However, the reason that you would have to make a choice between the two is with the existence of significant heterogeneity (Zhai and Guyatt, 2024). Heterogeneity in this context is statistical heterogeneity, defined as variability among studies (Higgins and Thomas, 2023). Significant heterogeneity is where the effects of the intervention across studies is more different from each other than expected by chance alone.

Assessing for heterogeneity before attempting meta-analysis is critical to choose the correct model. When studies are deemed to be statistically homogeneous, the fixed-effects model is usually used. Alternatively, when studies are deemed statistically heterogeneous then the random-effects model is used (Borenstein et al., 2010).

To assess whether heterogeneity is statistically significant, Cochran's Q test of homogeneity is employed.

$$H_0: The\ effect\ of\ moisturisers\ is\ equal\ across\ all\ studies.$$

$$H_1: The\ effect\ of\ moisturisers\ differs\ across\ all\ studies.$$

If the null hypothesis is rejected, the percentage of variance due to heterogeneity in meta-analysis is estimated for using the I^2 statistic. It is important to note that when the number of studies in meta-analysis is small, this statistic is susceptible to bias so using 95% confidence intervals is essential in reporting a more accurate I^2 (von Hippel, 2015).

Weight

Studies within a meta-analysis are not expected to hold equal significance. For example, a study conducted on a sample of size twenty is not going to be as robust as a study of size 300 simply by the existence of random variance. Thus, meta-analysis employs a strategy so that the effect of an underpowered study does not skew the overall effect. This strategy is known as weight. Weight quantifies each study into how reliable their effect size is. In a random-effect model, weight is only calculated using inverse variance. However, in a fixed-effect model, weight can be calculated using either inverse variance or Mantel-Haenszel. This choice depends on the sparsity of data. When event rates are low or study size is small, estimates used in the inverse variance methods may be poor (Higgins, J. and Thomas, J, 2023). Therefore, when data is sparse the Mantel-Haenszel method is preferred.

Besides seeing that a larger value of weight means that the study holds more weight, and a lower value means a study holds less weight, the exact numerical value of weight isn't as simple to understand as the weight percentage. So, weight can instead be reported as a percentage of how much each study impacted the overall effect of the meta-analysis.

Plots

Forest Plot

Forest plots can summarise almost all the essential information from a meta-analysis (Cochrane UK, 2019). They present the effect size of each study and their confidence intervals, whether a study is statistically significant, whether a study favours the intervention or control and lastly, the overall effect size. Therefore, being able to

understand a forest plot is important to taking in information from a meta-analysis with speed.

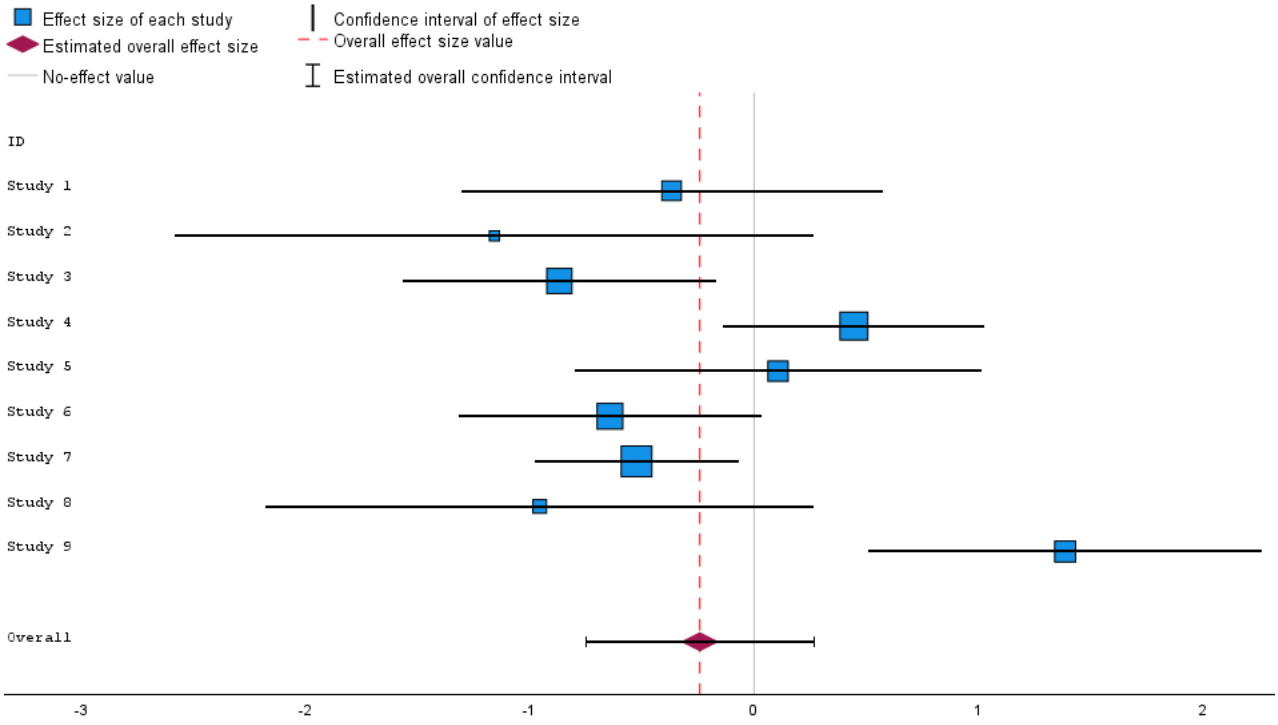

Figure 3: Example random-effect log odds ratio Forest Plot.

In Figure 3, each study is placed onto this log odds ratio scale as a blue square with the ID of the square marked to the left. The size of the blue square indicates the weight of the study. For example, study 7 has a large sample size so holds a lot of weight, so has a large square, meanwhile study 2, has a very low sample size so holds less weight resulting in a small square. The position of the square across the horizontal axis represents that studies effect size. Studies to the left of the null effect line (the line vertical from 0) favour the experimental group, while studies to the right favour the control group. The further a study is away from the null effect, the more it favours one side. When the studies confidence interval bar crosses the null effect line, the study is deemed not statistically significant. In this case, studies 3, 7 and 9 do not cross the null effect so are statistically significant. Lastly, the red diamond at the bottom indicates the overall effect size of all the combined studies and is where conclusions can be formed from a meta-analysis. This forest plot suggests that the overall effect is not statistically significant.

Funnel Plots

Publication bias is the problem that research with statistically significant results is more likely to be submitted, published, or published faster than non-significant results (Tatsioni, A. and Ioannidis J, 2017). Therefore, meta-analysis may end up being created using only studies with significant results leading to an overestimated result. As a result, Funnel plots are created to assess possible publication bias. Funnel plots are a type of scatter plot that compare the standard error against the effect size of each study. Ideally, each point should be spread evenly within the inverted funnel, however, an asymmetric funnel may suggest publication bias (Tatsioni, A. and Ioannidis J, 2017). The funnel arises from the fact that precision of the intervention effect increases as the study size increases.

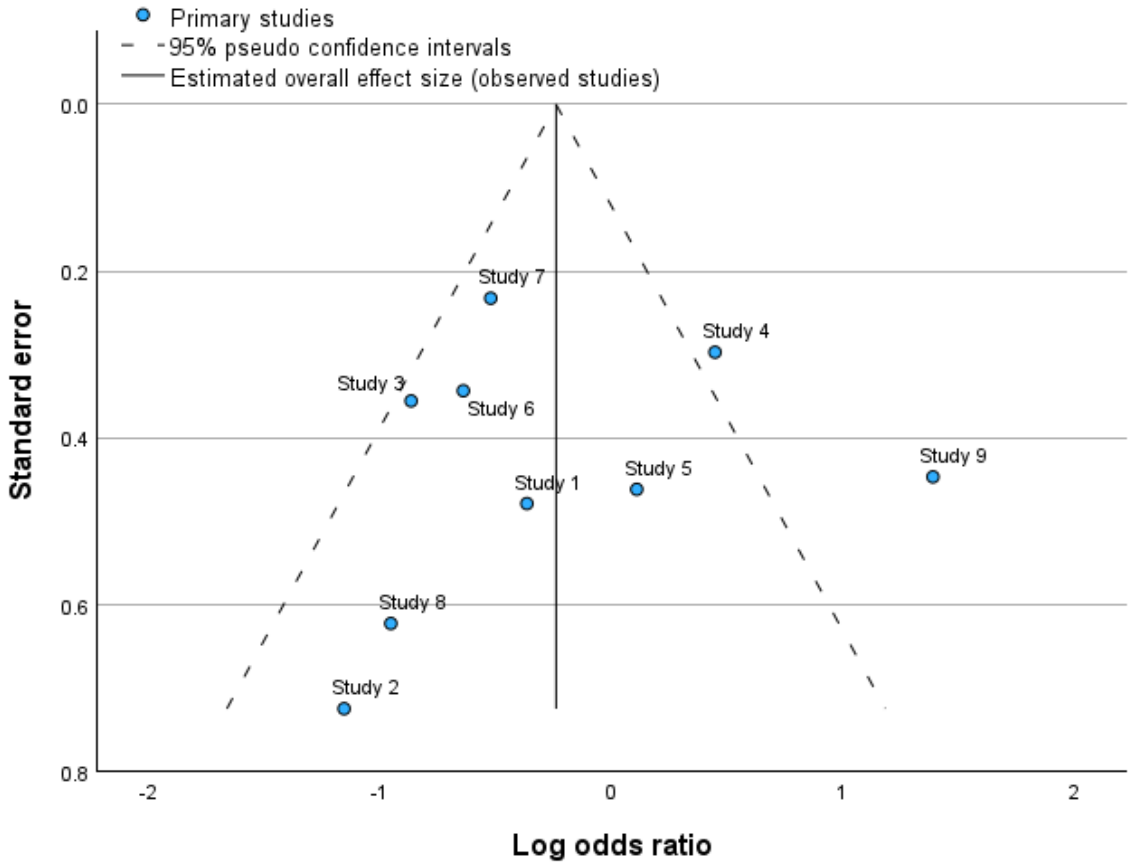

Figure 4: Example random-effect log odds ratio Funnel Plot

As seen in figure 4, the position of a study on the graph is dependent on the log odds ratio effect of the study and its weight, in this case it is standard error. The vertical line that the funnel is structured around indicates the overall effect of the study. The key feature to look out for within a funnel plot is symmetry. In this plot, there are studies missing from the bottom right of the funnel that are present in the bottom left (studies 8

and 2) creating an asymmetric plot. This suggests that the small studies that produced significant effects were published while other small studies producing non-significant effects were not published. One way of correcting the asymmetry created by publication bias while also estimating the number of missing studies is the trim and fill method. The basis of this method is to remove (trim) the studies believed to cause the asymmetry, then estimate the new true overall effect. Then, the omitted studies are added again (fill) with a counterpart predicted to have been removed because of publication bias. This method helps to visualise just where missing studies are expected to be.

However, funnel plot asymmetry should not always be equated with publication bias, particularly when there are a low number of studies (Higgins, J. and Thomas, J 2023). It is often recommended that conclusions can't be drawn from funnels with less than 10 studies since the power of the study will be too low and the existence of asymmetry could be attributed to multiple other possible causes (Sterne et al., 2011). It can be that asymmetry is merely by chance, or other forms of bias being introduced.

Alternative Plots

As mentioned previously, forest plots are the standard plot for illustrating meta-analysis. However, it is not the only plot able to do this. Two examples are the Galbraith plot and L'Abbe plot. Galbraith plots examine the z-statistic ($\frac{effect\ size}{standard\ error}$) against the standard error while L'Abbe plots examine the effect size of the treatment group against the effect size of the control group. These have the bonus of visualising heterogeneity, however, are not as easy to understand. Since heterogeneity can be examined for using Cochran's Q and the I^2 statistic, it is not deemed necessary at the cost of legibility. Another plot is the bubble plot. These plots are used during meta-regression as a way of assessing associations by study-level factors (Kiran, Crespillo and Rahimi, 2017). Study-level factors could include the size of the sample, the year of publication or duration of treatment.

Project Objectives

The Objective of this report is to use meta-analysis within IBM SPSS version 29 to determine the effectiveness of corticosteroids on atopic dermatitis. The choice of one

binary measure and one continuous measure was made to highlight the difference in techniques and results for these two types of meta-analysis.

Binary Measure: Number of participants experiencing a flare.

Continuous Measure: Change in disease severity.

Forming the Dataset

Data Sourcing

The data for performing this meta-analysis will be gathered from the databases of PubMed and Cochrane Library. PubMed is the United States owned National Library of medicine and comprises of more than 36 million citations for biomedical literature (National Library of Medicine, 2024). Cochrane is a global independent network of researchers, professionals, patients, carers, and people interested in health (Cochrane, 2022). Cochrane specialises in healthcare research using meta-analysis and systematic review.

Selecting the relevant and correct randomised controlled trials are essential as to not introduce bias into the meta-analysis. So, criteria are created to determine which meet the requirements to be included and those that do not.

Inclusion/Exclusion Criteria

Brennan (2023) defines the inclusion criteria as the elements of the randomised controlled trial that must be present to be eligible for inclusion and defines the exclusion criteria as the elements of the randomised controlled trial that disqualify the study from inclusion.

- Trial must measure the number of participants experiencing a flare and/or assessed on change in disease severity.
- Assessment of disease severity must be made using SCORAD, EASI or POEM.

Search Operation

Searching for studies was not limited by the number of available randomised controlled trials since eczema research is frequently release due to how common the condition is. But is instead limited by software and team a team made of 1 individual. Without access to automatic tools to find randomised controlled trials, the number of databases to

acquire RTCs had to be made small. Thus, each study was found individually and assessed for eligibility. Firstly, every study found to match the keywords were identified and set aside to be assessed. Duplicates between databases were found by comparing authors and date of publishing. Then, each trial was read briefly simply by title, or if necessary, abstract, to determine if they match the outcomes of this meta-analysis. Any that don't are then removed. Then, the included studies are assessed further to see if they meet the inclusion criteria. Studies that meet the inclusion criteria are included within this meta-analysis research. The keywords used to carry out the search were 'Atopic Dermatitis OR Eczema' and 'Moisturiser OR Corticosteroid'.

Results

Study Selection

PRISMA (2020), along with providing guidelines for performing meta-analysis also suggest the use of a flow diagram to present the process of study selection and in what area studies are removed.

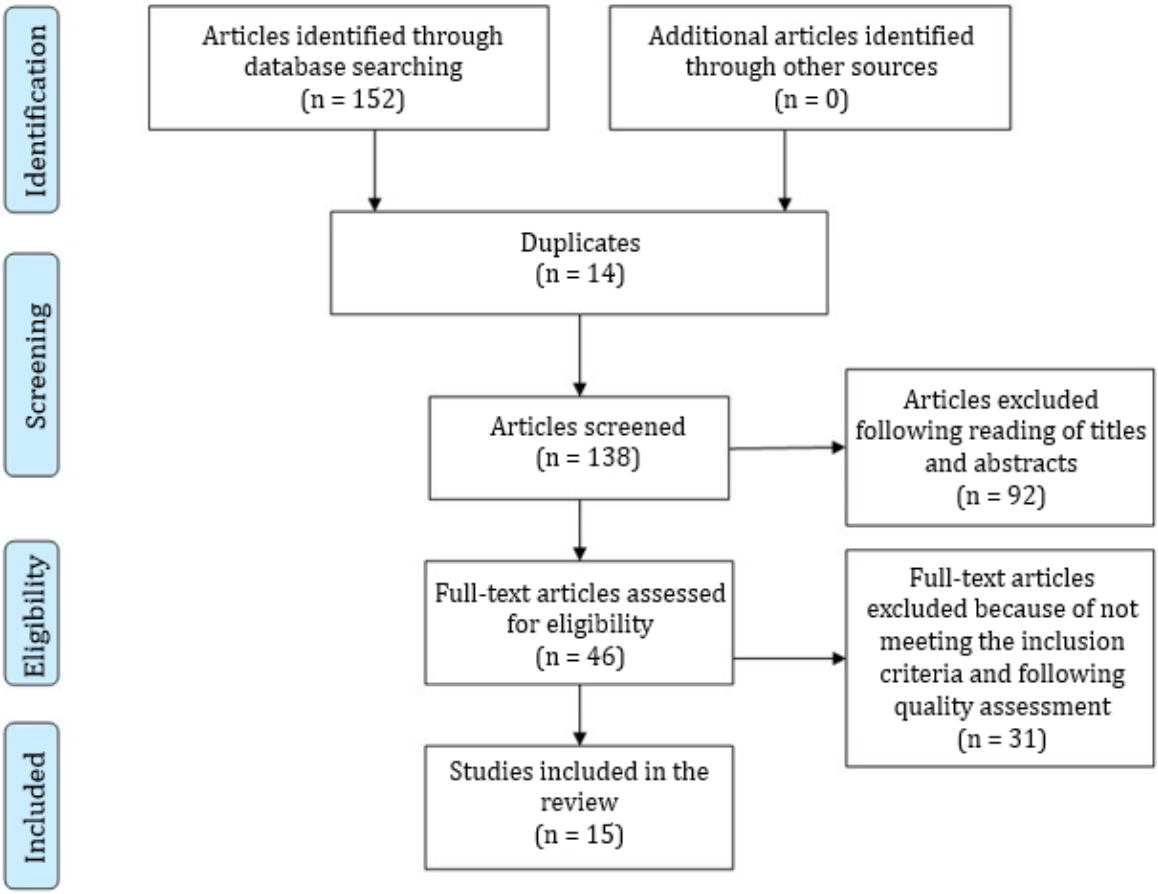

Figure 4: PRISMA (2020) designed flow diagram denoting the process of study selection.

Study Characteristics

This meta-analysis includes 15 studies. Nine studies (Abramovits 2008, Berth-Jones 2003, Boguniewicz 2008, Gayraud 2015, Glazenburg 2009, Hanifin 2002, Patrizi 2008, Weber 2015, and Wirén 2015) measured the number of participants experiencing a flare. While 6 studies (Giordano-Labadie 2006, Grimalt 2007, Msika 2008, Nebus 2009, Patrizi 2014, and Wu 2014) measured the change in disease severity.

For two studies it was possible to extract multiple sets of results which were found in Berth-Jones 2003 and Msika 2008. Berth-Jones 2003 examined the effects of two different corticosteroids against two different controls which allows this study to be split (presented in the data as Berth-JonesA and Berth-JonesB). Msika 2008 alternatively, examined the effects of a corticosteroid applied at different time points against different controls, again, allowing this study to be split (presented in the data as MsikaA and MsikaB). So, while technically belonging to the same study, for all intents and purposes, each will be referred to as their own study.

Of the nine studies comparing the number of participants experiencing a flare, the oldest study is Hanifin 2002, while the newest are Gayraud 2015 and Weber 2015. Based on the total number of participants in the studies, the largest study was Hanifin 2002 with 348, while the smallest was Patrizi 2008 with 39. Combining all the studies, data was taken from 1325 participants with 747 using the intervention and 578 from a control group.

Of the 6 studies measuring the change in disease severity, the oldest study is Grimalt 2007 while the newest are Patrizi 2014 and Wu 2014. The largest study was Grimalt 2007 with 148 participants while the smallest is MsikaA 2008 with 32 participants. In total, data was taken from 518 participants with 263 from the intervention group and 255 from the control group. Within each study, the mean change in disease severity for both the intervention and control groups were all negative. This means that on average the symptoms of eczema improved over the course of the research period regardless of the intervention, however, the difference in improvement will be assessed over this analysis.

Risk of Bias

The RoBvis (Risk of Bias Visualisation) tool, available to find at Cochrane (2019), allows the presentation of the risk of bias over several domains. Risk of bias is summarised into either High, Unclear or Low.

The domain numbers shown on the figures 3 and 4 represent a different area where bias may arise in a randomised controlled trial.

1) Random sequence generation
2) Allocation concealment
3) Blinding of participants and personnel
4) Blinding of outcome assessment
5) Incomplete outcome
6) Selective reporting
7) Other Bias

Where the final category (=) is the overall bias of the study.

Using the RoBvis tool, the risk of bias can be assessed across each of the 13 studies included in the meta-analysis.

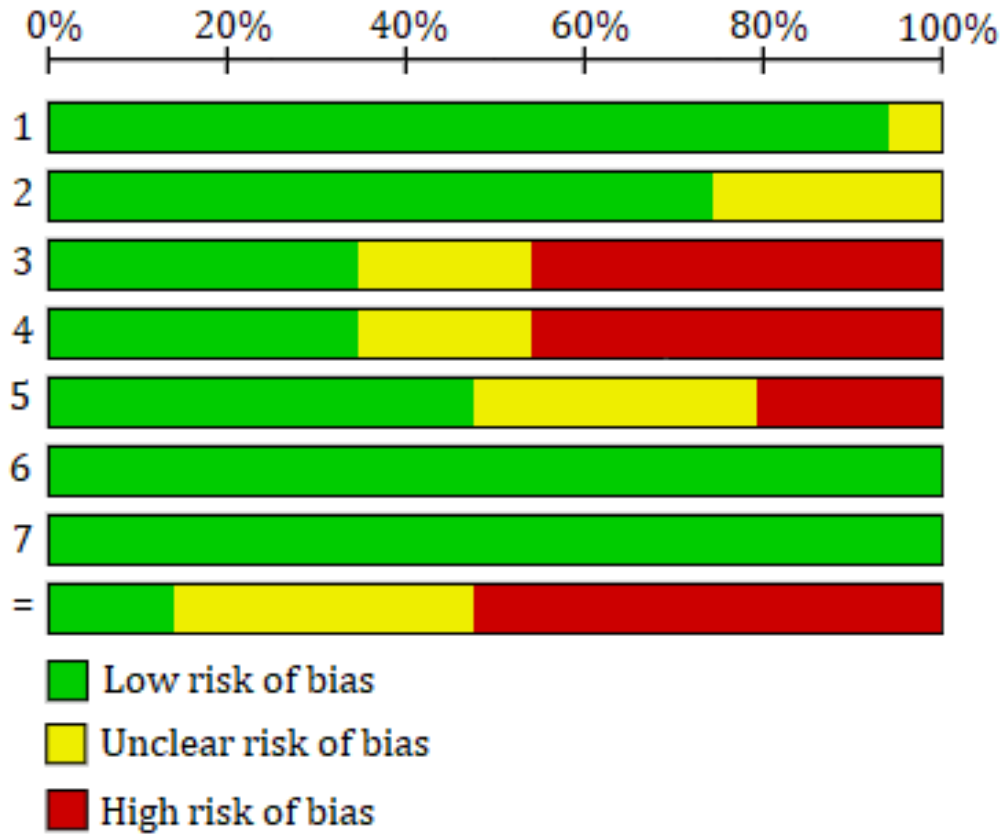

Figure 5:Weighted Bar plots of the distribution of risk of bias judgements for each bias domain.

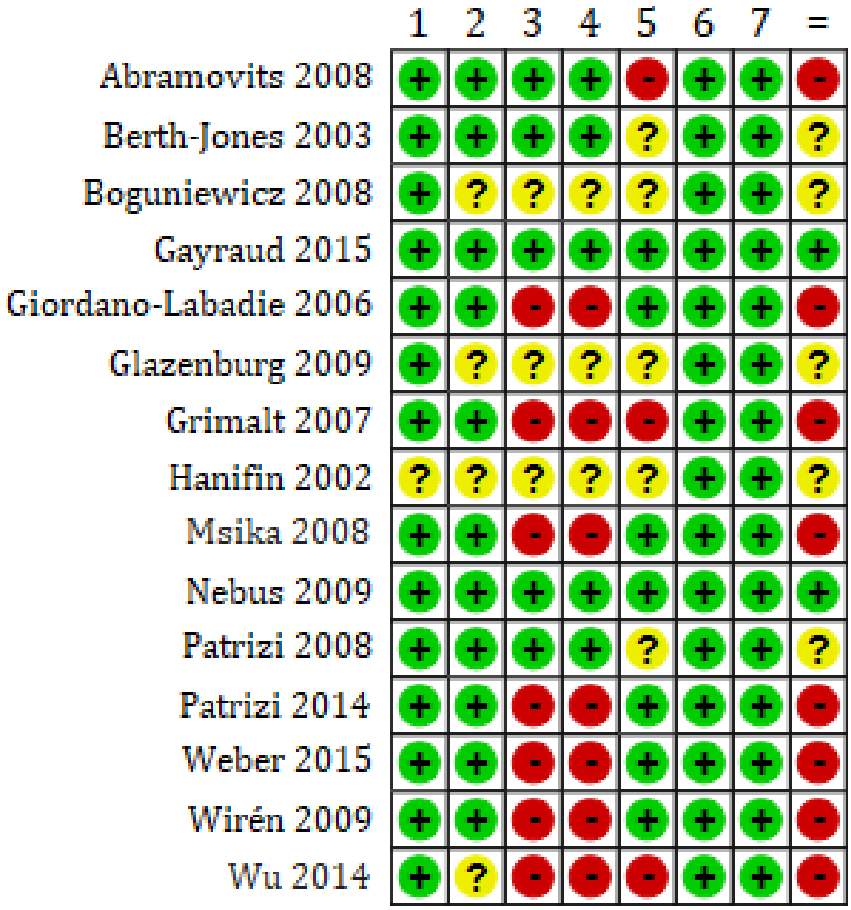

Figure 6:Traffic light plots of the domain-level judgements for each individual result.

Figure 5 represents the overall distribution of the levels of bias across the 7 categories. This is to help illustrate where bias is prevalent in this meta-analysis. Figure 6 represents the exact allocation of bias of every study for each category.

Studies with a low risk of bias showed a correct and clearly laid out method into their processes of reducing bias. Studies with an unclear risk of bias over any domain resulted from a lack of clarity into their methods that help reduce bias. Either not shown or do not provide in depth details into how they were performed. Lastly, studies with a high risk of bias showed that their methods to reduce bias either didn't exist or were described in a way that suggested it to be inadequate.

Seven studies presented a high risk of bias for blinding of participants and personnel and blinding of outcome assessment. Giordano-Labadie 2006, Grimalt 2007, Msika 2008, Patrizi 2014, Weber 2015, Wirén 2009, and Wu 2014 all lacked a suitable placebo, and all opted to provide the experimental group with the intervention and the control

group with nothing. Thus, leading to participants, personnel, and analysts to know the allocation.

Three studies presented a high risk of bias in the incomplete outcome domain. Abramovits 2008 had a high risk of bias because five patients from one group discontinued early due to not experiencing any positive result while zero patients from the other group discontinued early. This was explained in the experiment as participants dropping out due to lack of improvement, thus there will be lack of representation in the results for participants who had lower change in severity. Grimalt 2007 and Wu 2014 on the other hand, had a high loss to follow up across the whole study with a total of 25/173 and 20/125 participants dropping out respectively. This results in bias as there could be a noteworthy difference between the participants who leave and those who stay making it a less representative study.

The overall rating of the risk of the bias of a study is determined by the lowest ranking risk of bias in one of its domains. For example, Abramovits (2008) has a low risk of bias in 6 categories but a high risk of bias in just a single domain, so the overall study has a high risk of bias. The reason for this is because any potential introduction of bias affects the overall integrity of the study. To be clear, having a high risk of bias does not necessarily mean that a study is biased, but the results are more likely to be altered by bias than a study of lower risk of bias. Two studies resulted in a low risk of bias (Gayraud 2015 and Nebus 2009). Eight studies resulted in a high risk of bias (Abramovits 2008, Giordano-Labadie 2006, Grimalt 2007, Msika 2008, Patrizi 2014, Weber 2015, Wirén 2009, and Wu 2014). The last five studies resulted in an unclear risk of bias (Berth-Jones 2003, Boguniewicz 2008, Glazenburg 2009, Hanifin 2002, and Patrizi 2008).

Binary Measure

Binary measure meta-analysis is appropriate when the dependent variable is categorised into two groups. One of the variables selected to be analysed to determine the effectiveness of corticosteroids on atopic dermatitis is the number of participants who experience a flare while using the steroids compared to participants using a control. A flare is the return of eczema symptoms (WebMD, 2023). Thus, the categorised groups are either a participant experienced a flare or did not experience a flare.

The first step of performing the analysis is to select the effect size setting. Immediately, Peto's log odds ratio is unapplicable as the event rate is not small. From here, it is optional to select either the log odds ratio, log risk ratio or risk difference based on preference. This example will select the log odds ratio since it is the default SPSS option.

Secondly, heterogeneity must be tested for to determine whether the random or fixed effects model is appropriate. Application of Cochran's Q test for homogeneity determined that the studies are not homogeneous $Q(9) = 24.781, p = .003$. The I^2 test statistic provided by heterogeneity measures suggests that 63.7% of the variation across the study is due to heterogeneity rather than chance with a 95% confidence interval between 28.3% and 81.6%. Since heterogeneity statistically exists between studies, and is not small, the random-effects model is selected.

Table 1: Log odds ratio effect size of each study plus overall effect with standard errors, lower and upper 95% confidence intervals, p-values, and weight.

Study ID	Log Odds Ratio	Standard Error	Lower	Upper	P-Value	Weight	Weight (%)
Abramovits 2008	-2.47	0.44	-3.33	-1.61	0.00	1.9	11.03
BerthJonesA 2003	-2.07	0.38	-2.82	-1.32	0.00	2.07	12.04
BerthJonesB 2003	-0.67	0.34	-1.34	0.01	0.05	2.2	12.82
Boguniewicz 2008	-1.48	0.5	-2.47	-0.5	0.00	1.7	9.88
Gayraud 2015	-0.32	0.39	-1.08	0.44	0.41	2.06	11.97
Glazenburg 2009	-1.68	0.53	-2.72	-0.64	0.00	1.62	9.41
Hanifin 2002	-1.76	0.25	-2.24	-1.28	0.00	2.52	14.64
Patrizi 2008	-2.41	1.13	-4.62	-0.19	0.03	0.62	3.6
Weber 2015	-2.01	0.71	-3.41	-0.62	0.00	1.19	6.92
Wirén 2009	-1.52	0.65	-2.79	-0.26	0.02	1.32	7.7
Overall	-1.55	0.24	-2.02	-1.08	0.00		

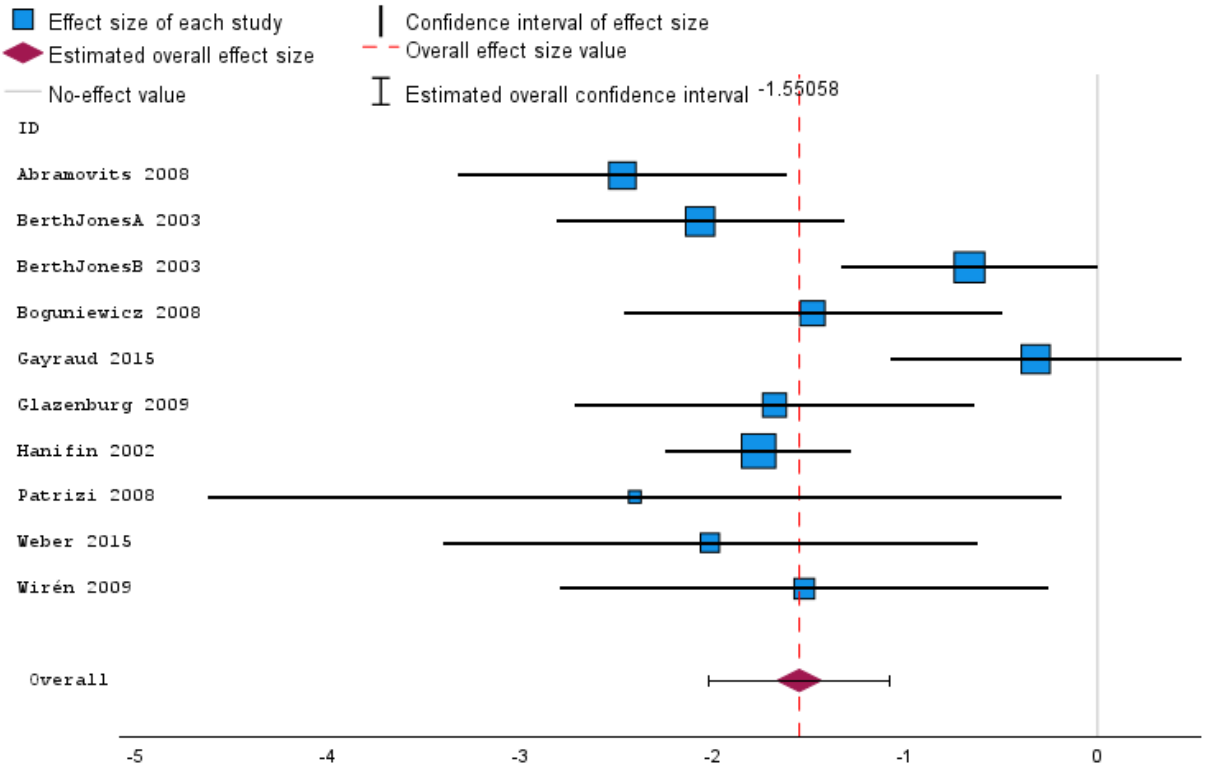

Figure 7: Random effects model forest plot comparing the log odds ratios effect size of each study.

All studies in the meta-analysis favoured the intervention group as each log odds ratio is left of the null effect line (log odds ratio is negative). Eight studies were statistically significant in finding that the intervention of the corticosteroid was more effective at reducing the number of participants experiencing a flare than those in the control group. However, Berth-JonesB 2003 ($p = 0.05$) and Gayraud 2015 ($p = 0.41$) were found to be statistically not significant in finding a difference between the intervention and control.

The study that held the most weight was Hanifin 2002 with a weight of 14.64%, while the study that held the least weight was Patrizi 2008 with a weight of 3.6%.

The overall effect of the meta-analysis determined that corticosteroids were statistically significant in reducing the number of participants experiencing a flare. The odds that a participant experienced a flare in the intervention group compared to the control was 21:100. Where the log odds ratio -1.55 (95% CI: -2.02 - -1.08, $p<0.005$).

With ten studies in the meta-analysis, it is appropriate to create a funnel plot to assess the existence of publication bias.

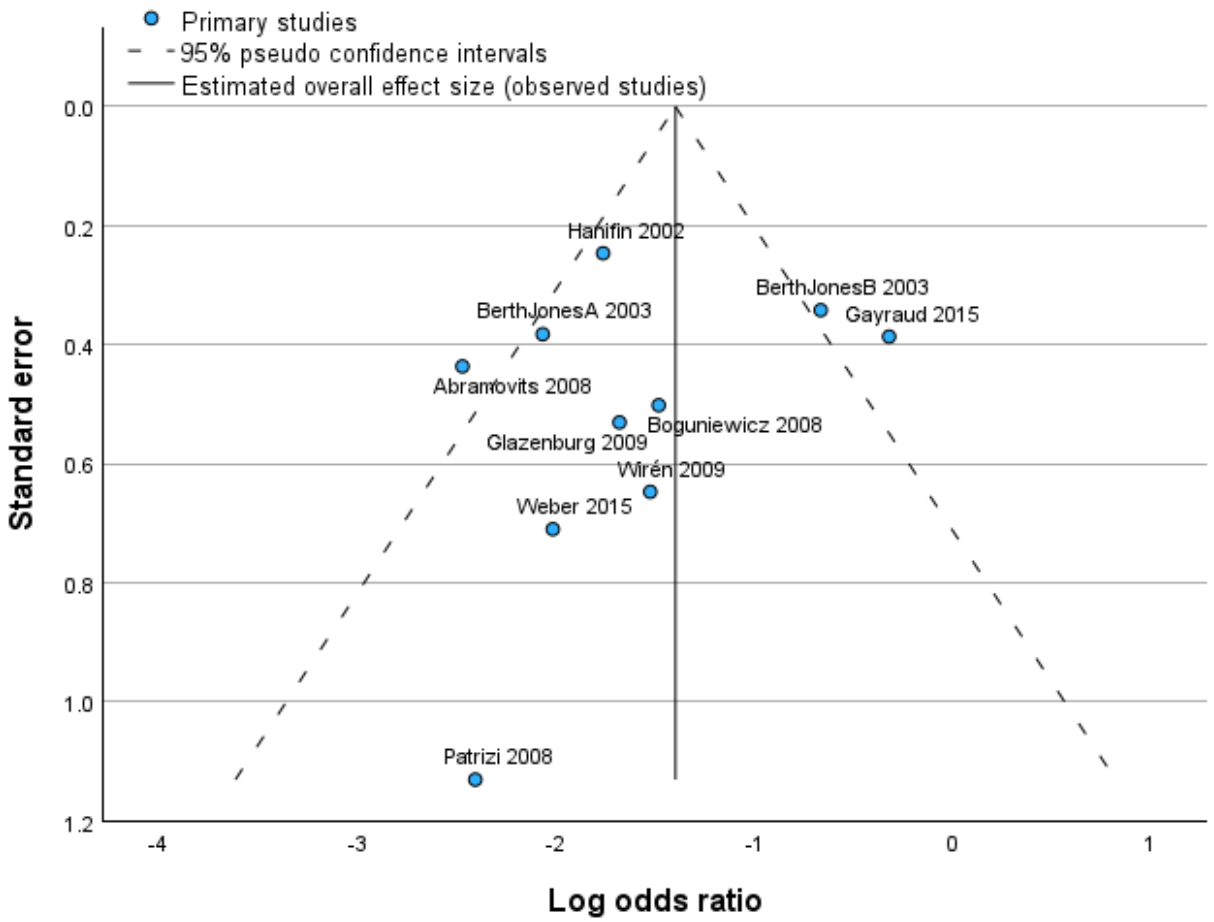

Figure 8: Random effects model funnel plot of the standard error against log odds ratio of each study.

This funnel plot shows an asymmetric design as the number of studies is not mirrored on either side nor evenly distributed. Since smaller studies have a large variation due to chance alone, it is expected that studies would be scattered around the bottom of the funnel, however, Patrizi 2008 is the only study located there and favours the intervention group. Publication bias could be a reason for this difference as small studies that provide non-significant results, are less likely to be published.

The trim-and-fill method is used to impute studies predicted to be omitted from the meta-analysis to illustrate where their results would sit on the funnel.

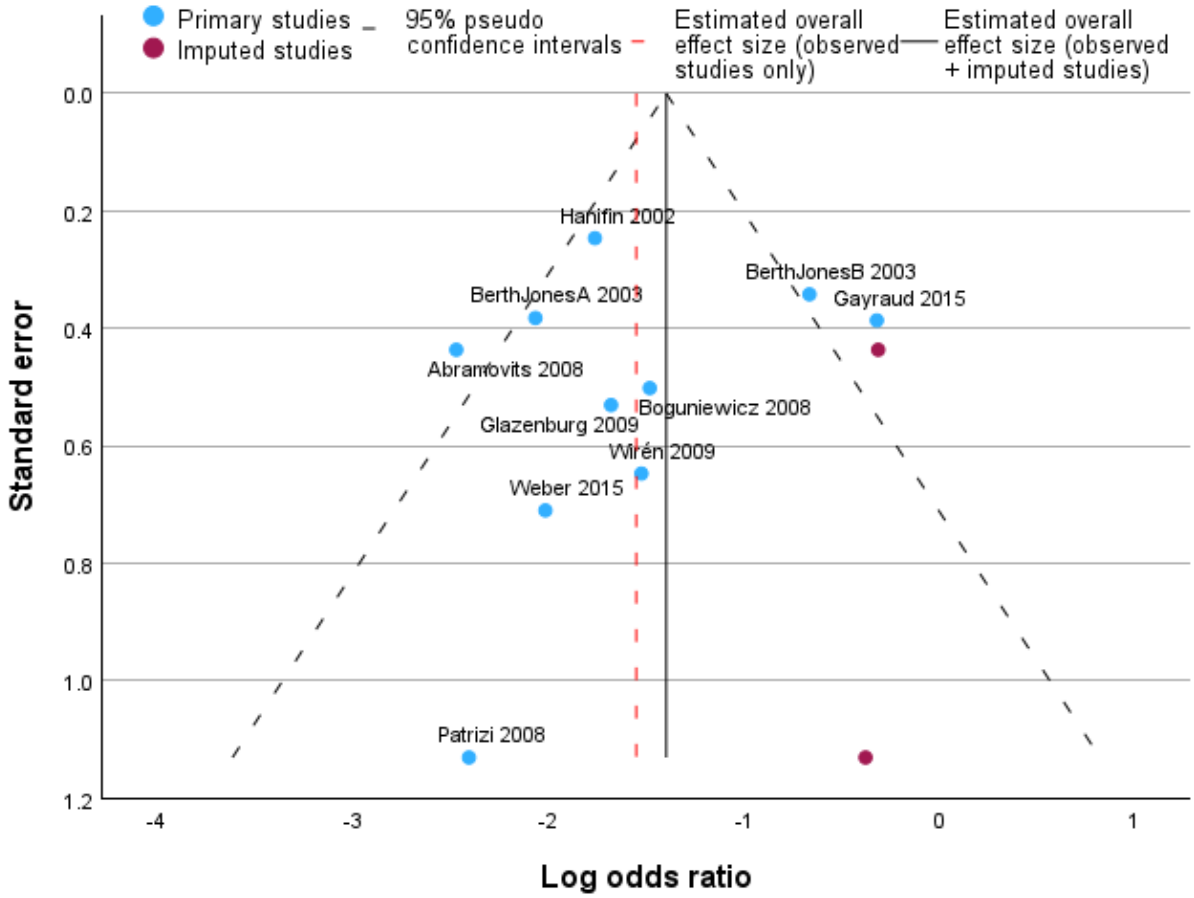

Figure 9: Random effects model funnel plot of the standard error against log odds ratio of each study with trim and fill imputed studies.

Applying trim-and-fill analysis imputed two statistically significant studies shown by the red points in figure 8. Applying the studies to the meta-analysis indicated that the overall effect size has shifted. The new overall log odds ratio effect size is -1.40 (95% CI: -1.86 - -0.93, $p<0.001$).

There is statistically significant evidence to suggest that corticosteroids are effective at reducing the number of participants experiencing a flare. The meta-analysis found that the odds that a participant experienced a flare in the intervention group compared to the control was 21:100. Upon application of the trim-and-fill, the odds that a participant experienced a flare in the intervention group compared to the control increase to 24:100.

Continuous Measure

Continuous measure meta-analysis is appropriate when the dependent variable is presented as a mean value with its standard deviation. So, the other variable selected to be analysed to determine the effectiveness of corticosteroids on atopic dermatitis is the change in disease severity measured by either SCORAD, EASI or POEM compared to participants using a control.

To determine the effect size setting for a continuous measure is less preference focused than a binary measure and is more dependent on the nature of the meta-analysis. Firstly, the effect size must be standardised since some studies use EASI and others use SCORAD to rate the change in disease severity. Thus, the unstandardised mean difference is removed as an option. Next, Hedges' g can be removed since not one study has a size of less than 20. Since the variation between the intervention and control is not expected to be unequal given the nature of the data, Cohen's d is selected.

Heterogeneity must be tested for to determine whether the random or fixed effects model is appropriate. Application of Cochran's Q test for homogeneity determined that the studies are not homogeneous $Q(6) = 24.688, p = < 0.001$. I^2 test statistic provided by heterogeneity measures suggests that 75.7% of the variation across the study is due to heterogeneity rather than chance with a 95% confidence interval between 48.7% and 88.5%. Since heterogeneity statistically exists between studies, and is not small, the random-effects model is selected.

Table 2: Cohen's d effect size of each study plus overall effect with standard errors, lower and upper 95% confidence intervals, p-values, and weight.

Study ID	Cohen's d	Standard Error	Lower	Upper	P-Value	Weight	Weight (%)
Giordano-Labadie 2006	-0.69	0.24	-1.16	-0.22	0.00	4.65	15.21
Grimalt 2007	-0.02	0.16	-0.35	0.30	0.89	5.41	17.70
MsikaA 2008	-0.82	0.37	-1.54	-0.10	0.03	3.40	11.14
MsikaB 2008	-0.51	0.34	-1.18	0.17	0.14	3.63	11.87
Nebus 2009	0.01	0.28	-0.55	0.56	0.98	4.21	13.77
Patrizi 2014	-1.12	0.29	-1.69	-0.55	0.00	4.10	13.44
Wu 2014	-1.01	0.19	-1.39	-0.64	0.00	5.16	16.88
Overall	-0.58	0.18	-0.94	-0.23	0.00		

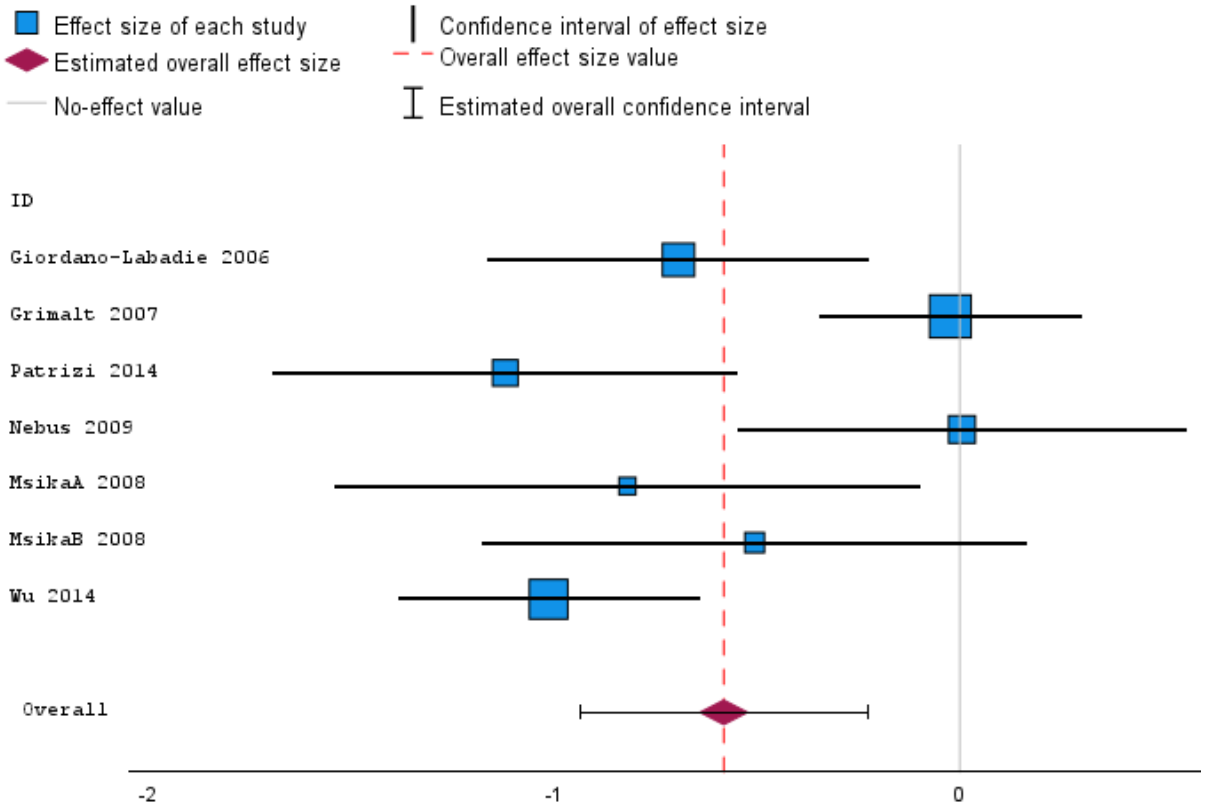

Figure 10:Random effects model forest plot comparing the Cohen's d effect size of each study.

Four studies were statistically significant in finding that the intervention of the corticosteroid was more effective at reducing the severity of eczema than the control. While Grimalt 2007 (p = 0.89), Nebus 2009 (p = 0.98), and MsikaB 2008 (p = 0.14) were produced a statistically non-significant effect.

The study that held the most weight was Grimalt with a weight of 17.70%, while the study that held the least weight was MsikaA with a weight of 11.14%.

The overall meta-analysis determined that corticosteroids were statistically significant in reducing the severity of eczema more than the control by a medium effect. -0.58 (95% CI: -0.94 - -0.23, p<0.005).

Meta-analyses are conclusive with as little as two studies, however, not all in-depth analysis can be carried out. This meta-analysis contained 7 studies, so creating a funnel plot to assess potential publication bias is not necessarily appropriate as any variation has a high likelihood to be from chance alone.

Discussion

Summary of Results

Through performing binary measure meta-analysis on a selection of ten studies each analysing the effectiveness of corticosteroids on atopic dermatitis, it was deemed that there was a statistically significant decrease in the odds that a patient would experience a flare when applying corticosteroids compared to the control. The estimated odds that a participant would experience a flare when applying the corticosteroid compared to the control was 21:100 (Log odds ratio = -1.55 (95% CI: -2.02 - -1.08, $p<0.005$)). After the application of the trim-and-fill method to detect potential publication bias, the estimated odds that a participant would experience a flare when applying the corticosteroids compared to the control was 24:100 (Log odds ratio = -1.40 (95% CI: -1.86 - -0.93, $p<0.001$)).

Performing the continuous measure meta-analysis on a selection of 7 studies found that there was a statistically significant decrease in the severity of symptoms of atopic dermatitis. The application of corticosteroids determined there to be a medium sized effect decrease in severity of symptoms compared to a control (Cohen's d = -0.58 (95% CI: -0.94 - -0.23, $p<0.005$)).

In conclusion, there is sufficient evidence to suggest that corticosteroids are effective at reducing the frequency and severity of eczema symptoms.

Strength and Limitations

Strengths

Meta-analysis is at the top of the hierarchy of evidence pyramid for a reason. Being able to take the greatest statistical power of primary research, in the form of randomised controlled trials, and combining them to form accurate estimates for the effect of an intervention is extremely valuable to any evidence-based clinical research.

It is likely that an individual RTC is only able to take participants from the population of a specific area, often with similar demographics and characteristics. However, by combining several studies each with their own unique demographics, a more generalisable effect can be calculated. This means that the estimates concluded by meta-analysis can be more applicable to a wider population.

Meta-analysis can create new use for studies too small to detect any statistically significant effect by using them to help calculate the new estimated overall effect. While at the same time, weight calculations prevent these smaller studies from harshly skewing the results that larger, more robust studies can provide.

Using common meta-analysis plots such as forest and funnel, trends and patterns in data such as heterogeneity or the presence of publication bias can be found to help researchers assess the validity of the data and help researchers identify where any variability may arise.

Limitations

The quality of a meta-analysis depends on the quality of randomised controlled trials found. In a perfect world, only studies that illustrate the steps performed to result in a low risk of bias would be included into a meta-analysis, but in that case, it would be hard to find enough trials to form any statistically viable conclusions for almost any meta-analysis in clinical research. Thus, studies that have an unclear or high risk of bias are often included into meta-analysis. When the studies that show a higher risk of bias are included, it is important to notice whether their results appear abnormally large or small, or whether they fail to follow trends between studies to ensure that the overall meta-analysis is not influenced too heavily by these potential biases.

During analysis of the binary measure, application of the funnel plot indicated that there was potential for publication bias. This could mean that the overall effect is an overestimate of the effectiveness of corticosteroids. So, the trim-and-fill method was applied in attempts to correct this. However, if the funnel plot was shaped asymmetrically due to chance variation alone, then the new overall effect could be an underestimate of the effectiveness of corticosteroids.

Using Cochran's Q and the I^2 statistic, it was found in both the continuous and binary measure that heterogeneity was present. However, meta-analysis cannot explain this heterogeneity and determining where this arises can be difficult. It could be from, but not limited to, variation in study design, populations of participants, or differences in the type of corticosteroid.

There were limitations through carrying out the analysis in IBM SPSS version 29. Meta-analysis is not typically performed using this software and guidelines into how to

perform meta-analysis, such as the one provided by IBM (2023) do not give reasonings as to when and why specific settings should be applied. For example, the meta-analyses performed by Cochrane (2020) use software called Review Manager (RevMan) which provide in-depth methodologies, more advanced settings, and alternative methods to calculate effect size. Using this would be preferred, however, is not freely available to use.

Implications of Research

Understanding the exact improvements that corticosteroids can make in reducing the effects of the symptoms of eczema can help justify their use for sufferers. Often, people with eczema must weigh up the benefits vs the side-effects of corticosteroids on the skin with such adverse effects including bruising, skin thinning, and acne (Yasir et al., 2021). Additionally, prolonged use of corticosteroids can lead to harsh withdrawal symptoms when stopped. A suggestion for further research could therefore relate to the prevalence of such side effects or withdrawals upon corticosteroid usage.

Additionally, the limited tools to help perform meta-analysis when using SPSS opens suggestions into whether more comprehensive guidelines should be produced, ones that carefully but simply explain when and where to apply specific settings, the appropriate usage of graphics and all the available features, and where to find the necessary tools to check any assumptions and heterogeneity.

Reflection

I am extremely pleased with the work put forward over the course of this project. By applying my favourite mathematical subject of statistics to data relating to a condition that I have lived my day-to-day life with has been a rewarding and insightful experience. Learning about the process of meta-analysis, a form of analysis I had never heard of before taking up this project, and its importance within the health-care world has been eye-opening. The methodologies and processes of meta-analysis I have had to break down and simplify to make the techniques digestible will enable me to approach unfamiliar analyses with a newfound confidence.

I believe I was able to produce reliable results and clearly laid out methods into how these results were synthesised with justifications for processes and the importance of

specific steps performed within randomised controlled trials and systematic review to produce a reliable meta-analysis.

I was made aware by my project supervisor of the existence of meta-analysis and systematic review as two appropriate forms of analyses to tackle my original research question relating to the effectiveness of general treatments for eczema, which was quickly refined to just corticosteroids. I learned that plenty of students at UWE perform systematic reviews, however, meta-analysis was far more uncommon. Thus, I challenged myself to take on meta-analysis and learn about this statistical method to prove that I was able to single-handedly develop new skills and techniques.

Across learning about meta-analysis and its importance to evidence-based research, especially since it has been shown to be the most frequently cited form of clinical research (Haidich, 2010), there is argument to suggest teaching the processes of systematic review and meta-analysis at UWE would be extremely valuable to students within mathematics who are entering the professional world. Therefore, I would personally recommend its inclusion into future statistics modules.

Study References

Abramovits, W. (2006) A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. Journal of drugs in dermatology: JDD [online]. 5 (3), pp. 236–244. Available from: https://pubmed.ncbi.nlm.nih.gov/16573256/ [Accessed 10 March 2024]

Berth-Jones, J. (2003) Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ [online]. 326 (7403). [Accessed 10 March 2024]

Boguniewicz, M. (2008) MAS063DP is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study. The Journal of Pediatrics [online]. 152 (6), pp. 854–859. [Accessed 10 March 2024]

Gayraud, F. (2015) Efficacy and tolerance assessment of a new type of dermocosmetic in infants and children with moderate atopic dermatitis. Journal of Cosmetic Dermatology [online]. 14 (2), pp. 107–112. [Accessed 10 March 2024]

Giordano-Labadie, F. (2006) Evaluation of a new moisturizer (Exomega milk®) in children with atopic dermatitis. Journal of Dermatological Treatment [online]. 17 (2), pp. 78–81. [Accessed 10 March 2024]

Glazenburg, E.J. (2009) Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: Differences between boys and girls? Pediatric Allergy and Immunology [online]. 20 (1), pp. 59–66. [Accessed 10 March 2024]

Grimalt, R. (2006) The Steroid-Sparing Effect of an Emollient Therapy in Infants with Atopic Dermatitis: A Randomized Controlled Study. Dermatology [online]. 214 (1), pp. 61–67. [Accessed 10 March 2024]

Hanifin, J. (2002) Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. British Journal of Dermatology [online]. 147 (3), pp. 528–537. [Accessed 10 March 2024]

Msika, P. (2008) New Emollient with Topical Corticosteroid-Sparing Effect in Treatment of Childhood Atopic Dermatitis: SCORAD and Quality of Life Improvement. Pediatric Dermatology [online]. 25 (6), pp. 606–612. [Accessed 10 March 2024]

Nebus, J. (2009) A daily oat-based skin care regimen for atopic skin. Journal of the American Academy of Dermatology [online] 62 (2), pp. AB67. [Accessed 10 March 2024]

Patrizi, A. (2008) A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIRTM) in the management of atopic dermatitis in paediatric patients. [online]. 0 (0), p. 080220191244231-??? [Accessed 10 March 2024]

Patrizi, A. (2016) Effects of a New Emollient-Based Treatment on Skin Microflora Balance and Barrier Function in Children with Mild Atopic Dermatitis. Pediatric Dermatology [online]. 33 (2), pp. 165–171. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5071726/ [Accessed 10 March 2024]

Weber, T.M. (2015) Steroid-Free Over-the-Counter Eczema Skin Care Formulations Reduce Risk of Flare, Prolong Time to Flare, and Reduce Eczema Symptoms in Pediatric Subjects With Atopic Dermatitis. Journal of drugs in dermatology: JDD [online]. 14 (5), pp. 478–485. [Accessed 10 March 2024]

Wirén, K. (2009) Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. Journal of the European Academy of Dermatology and Venereology [online]. 23 (11), pp. 1267–1272. [Accessed 10 March 2024]

Wu, Y-Q. (2014) Clinical observation of moisture and softening cream (MSC) combined with compound flumetasone ointment for chronic eczema. Journal of Clinical Dermatology 42(7), pp. 434-6. [Accessed 10 March 2024]

Bibliography

Ahn, E. and Kang, H. (2018) Introduction to Systematic Review and meta-analysis. *Korean Journal of Anesthesiology* [online]. 71 (2), pp. 103–112. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5903119/. [Accessed 8 March 2024].

Barrett, D. and Noble, H. (2019) What are cohort studies? *Evidence Based Nursing* [online]. 22 (4), pp. 95–96. Available from: https://ebn.bmj.com/content/22/4/95. [Accessed 6 March 2024].

Borenstein, M., Hedges, L.V., Higgins, J.P.T. and Rothstein, H.R. (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods [online]. 1 (2), pp. 97–111. [Accessed 19 March 2024].

Brennan, E. (2023) *Guides: Systematic reviews: Inclusion/Exclusion criteria musc.libguides.com*. [online]. Available from: https://musc.libguides.com/systematicreviews/eligibilitycriteria#loaded. [Accessed 8 March 2024].

CKS (2022) *NICE*. 2022 [online]. Available from: https://cks.nice.org.uk/topics/eczema-atopic/prescribing-information/topical-corticosteroids/. [Accessed 2 February 2024].

Cochrane (2016) *Meta-analysis: What, Why, and How uk.cochrane.org*. [online]. Available from: https://uk.cochrane.org/news/meta-analysis-what-why-and-how. [Accessed 13 February 2024].

Cochrane (2019). *RoB 2: A revised Cochrane risk-of-bias tool for randomized trials*. [online] Cochrane.org. Available at: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials. [Accessed 15 March 2024].

Cochrane (2022). *What is Cochrane?* [online] Available at: https://www.cochrane.org/news/what-cochrane. [Accessed 9 March 2024].

Cochrane UK (2019) How to read a forest plot? Cochrane.org. [online]. Available from: https://uk.cochrane.org/news/how-read-forest-plot. [Accessed 26 March 2024].

Ganesan, P. (2022) How to write case reports and case series. *International Journal of Advanced Medical and Health Research* [online]. 9 (1), p. 55. [Accessed 6 March 2024]

Ganeshkumar, P. and Gopalakrishnan, S. (2013) Systematic Reviews and meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care* [online]. 2 (1), pp. 9–14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3894019/. [Accessed 15 March 2024].

George, T. (2022) *What Is an Observational Study? Scribbr*. [online]. Available from: https://www.scribbr.com/methodology/observational-study/. [Accessed 5 March 2024].

Haidich, A.B. (2010) Meta-analysis in medical research. *Hippokratia* [online]. 14 (Suppl 1), pp. 29–37. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049418/#:~:text=Hierarchy%20of%20evidence [Accessed 13 April 2024].

Hassan, M. (2022) *Primary Data - Types and Methods Research Method*. [online]. Available from: https://researchmethod.net/primary-data/. [Accessed 7 March 2024].

Shorten, A. and Shorten, B. (2012). What is meta-analysis? *Evidence Based Nursing*, [online] 16(1), pp.3–4. doi: https://ebn.bmj.com/content/16/1/3 [Accessed 8 March 2024].

Hassan, M. (2022) *Secondary Data - Methods and Types Research Method*. [online]. Available from: https://researchmethod.net/secondary-data/. [Accessed 5 March 2024].

Higgins, J. and Thomas, J. (2023). Cochrane Handbook for Systematic Reviews of Interventions. [online] Cochrane.org. Available at: https://training.cochrane.org/handbook/current. [Accessed 20 March 2024].

IBM (2023) Meta-Analysis [online] Available from: https://www.ibm.com/docs/en/spss-statistics/saas?topic=features-meta-analysis. [Accessed 5 April 2024].

Kiran, A., Crespillo, A.P. and Rahimi, K. (2017). Graphics and Statistics for Cardiology: Data visualisation for meta-analysis. *Heart*, [online] 103(1), pp.19–23. doi:https://doi.org/10.1136/heartjnl-2016-309685. [Accessed 28 March 2024].

Lim, C.-Y. and In, J. (2019) Randomization in Clinical Studies. *Korean Journal of Anesthesiology* [online]. 72 (3), pp. 221–232. Available from:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6547231/. [Accessed 14 February 2024].

Mack, M.R. and Kim, B.S. (2018) The Itch–Scratch Cycle: A Neuroimmune Perspective. *Trends in Immunology* [online]. 39 (12), pp. 980–991. Available from: https://www.sciencedirect.com/science/article/pii/S1471490618301856. [Accessed 13 February 2024].

Mcleod, S. (2019). *Sampling Distribution*. [online] Simplypsychology.org. Available at: https://www.simplypsychology.org/effect-size.html. [Accessed 19 March 2024].

Medical News Today (2022) 'Eczema, gut health, and the microbiome: Is there a link?'. [online]. Available from: https://www.medicalnewstoday.com/articles/eczema-gut-health. [Accessed 3 February 2024].

Murad, M.H., Asi, N., Alsawas, M. and Alahdab, F. (2016) New Evidence Pyramid. *Evidence Based Medicine* [online]. 21 (4), pp. 125–127. [Accessed 5 March 2024].
National Eczema Association (2013) *Types of Eczema | National Eczema Association National Eczema Association*. 2013 [online]. Available from: https://nationaleczema.org/eczema/types-of-eczema/. [Accessed 12 February 2024].

National Eczema Society (2019) *Information and advice National Eczema Society*. [online]. Available from: https://eczema.org/information-and-advice/. [Accessed 3 February April 2024].

National Library of Medicine (2024) *PubMed Labs PubMed Labs*. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/. [Accessed 9 March 2024].

NHS (2019) *Treatment - Atopic eczema NHS*. 2019 [online]. Available from: https://www.nhs.uk/conditions/atopic-eczema/treatment/. [Accessed 12 February 2024].

NHS (2019). *Overview - Atopic Eczema*. [online] NHS. Available at: https://www.nhs.uk/conditions/atopic-eczema/. [Accessed 12 February 2024].

Oakley, A. (2009). SCORAD (scoring atopic dermatitis) | DermNet. NZ [online] Available from: https://dermnetnz.org/topics/scorad#:~:text=SCORAD%20is%20a%20clinical%20tool. [Accessed 30 March 2024].

Oakley, A. (2015) EASI score. Eczema area and severity index | DermNet NZ dermnetnz.org. 2015 [online]. Available from: https://dermnetnz.org/topics/easi-score. [Accessed 30 March 2024].

PRISMA (2020) *PRISMA Prisma-statement.org*. 2020 [online]. Available from: http://www.prisma-statement.org/. [Accessed 8 March 2024].

Roberts, C. and Torgerson, D. (1998) Understanding controlled trials: Randomisation methods in controlled trials. *BMJ* [online]. 317 (7168), pp. 1301–1310. [14 February 2024].

Schulz, K.F. and Grimes, D.A. (2002) Unequal group sizes in randomised trials: guarding against guessing. *Lancet (London, England)* [online]. 359 (9310), pp. 966–70. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11918933. [Accessed 14 February 2024].

Seladi-Schulman, J. (2020) *Placebo Effect: What It Is, Examples, and More Healthline*. [online]. Available from: https://www.healthline.com/health/placebo-effect. [Accessed 18 February 2024].

Shorten, A. and Shorten, B. (2012). What is meta-analysis? *Evidence Based Nursing*, [online] 16(1), pp.3–4. doi: https://ebn.bmj.com/content/16/1/3 [Accessed 8 March 2024].

Sterne, J.A.C. *et al.* (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* [online]. 343, p. d4002. Available from: https://www.bmj.com/content/343/bmj.d4002. [Accessed 27 March 2024].

Stephanie (2016). *Hedges' g: Definition, Formula*. [online] Statistics How To. Available at: https://www.statisticshowto.com/hedges-g/. [Accessed 18 March 2024].

Stephanie (2017). Glass's Delta. [online] Statistics How To. Available at: https://www.statisticshowto.com/glasss-delta/. [Accessed 18 March 2024].

Tatsioni, A. and Ioannidis J. (2017). *Funnel Plot - an overview | ScienceDirect Topics*. [online] Available at: https://www.sciencedirect.com/topics/medicine-and-dentistry/funnel-plot#:~:text=In%20a%20funnel%20plot%2C%20the. [Accessed 27 March 2024].

Tenny, S., Kerndt, C.C. and Hoffman, M.R. (2023) *Case Control Studies PubMed*. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/28846237/. [Accessed 6 March 2024].

The University of Nottingham (n.d.). Patient Oriented Eczema Measure - The University of Nottingham. [online] Available from: https://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx. [Accessed 31 March 2024].

Thomas, L. (2020) *How to use stratified sampling Scribbr*. [online]. Available from: https://www.scribbr.com/methodology/stratified-sampling/. [Accessed 15 February 2024].

Thomas, L. (2020) *What is a Double-Blind Study? | An Easy Introduction to Blinding Scribbr*. [online]. Available from:

https://www.scribbr.com/methodology/double-blind-study/. [Accessed 18 February 2024].

Viera, A. (2008) *Odds Ratios and Risk Ratios: What's the Difference and Why Does It Matter? Southern medical journal*. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/18580722/. [Accessed 16 March 2024].

von Hippel, P.T. (2015). The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Medical Research Methodology*, 15(1). doi: https://doi.org/10.1186/s12874-015-0024-z. [Accessed 25 March 2024].

WebMD (2023) WebMD [online]. Available from: https://www.webmd.com/skin-problems-and-treatments/eczema/live-better-eczema. [Accessed 30 March 2024].

Yasir, M., Goyal, A., Bansal, P. and Sonthalia, S. (2021) *Corticosteroid Adverse Effects PubMed*. [online]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531462/#:~:text=%5B13%5D%20These%20adverse%20effects%20include. [Accessed 12 April 2024].

Zhai, C. and Guyatt, G. (2024) Fixed-effect and random-effects models in meta-analysis. *Chinese Medical Journal* [online]. 137 (1), p. 1. Available from: https://journals.lww.com/cmj/fulltext/2024/01050/fixed_effect_and_random_effects_models_in.1.aspx. [Accessed 19 March 2024].