Abstract: Strongyloidiasis is a helminth infection that remains under-researched despite its ability to cause significant illness. Women and children may be at particular risk of health consequences from this parasite. This systematic literature review aims to examine research on the long-term health effects that strongyloidiasis has in pregnant women and children. We conducted a structured search using multiple databases to collect all primary studies discussing health effects of strongyloidiasis in the aforementioned groups. The review included 20 results: 16 primary studies and four case reports. The methodological quality of studies was substandard, and there was substantial heterogeneity to the statistical analysis and outcomes assessed in the literature. Statistically significant associations were found between strongyloidiasis and low birth weight, as well as wasting. No links were found between strongyloidiasis and anaemia. Due to testing methods used in the studies, the prevalence of Strongyloides stercoralis in these studies was probably underestimated. Current research is suggestive that strongyloidiasis has long-term adverse health effects on the offspring of infected mothers and in chronically-infected children. Data analysis was hindered by both methodological and statistical flaws, and as such, reliable conclusions regarding the health impacts could not be formed.

Keywords: Strongyloidiasis; low birth weight; wasting

1. Introduction

Strongyloidiasis is a Neglected Tropical Disease (NTD) caused by the infection of a host with the soil-transmitted nematode of the Strongyloides genus. Humans are most commonly infected by S. stercoralis. However, S. fuelleborni has also been observed to infect humans in Papua New Guinea (PNG). S. stercoralis is believed to infect over 370 million people worldwide [1].

Strongyloidiasis was originally identified as a disease to look for primarily in returned travellers, refugees, or war veterans [2,5]. The life cycle of S. stercoralis grants it the ability to autoinfect hosts, thereby allowing the parasites to persist chronically in individuals. The parasite was believed to exist in the small intestines of hosts in a predominantly asymptomatic state, but it occasionally caused low-grade epigastric pain and diarrhoea. Studies have instead shown that intermittently symptomatic strongyloidiasis is more common than asymptomatic infection [4]. As more precise serological tests are being developed, recent data is showing that the prevalence of Strongyloides infections remains consistently underestimated [2,5].

There are a variety of testing methods currently utilised to detect S. stercoralis infection. However, they differ greatly in their accuracy [6]. The current gold standard as recognised by the Centers for Disease Control and Prevention (CDC) is seven stool samples using specialised testing techniques such as the Baermann concentration or nutrient agar plate cultures [7]. While studies typically relied on stool samples, modern serological techniques have been proven to be more accurate and practical for use in research [8].
Strongyloidiasis has also been associated with life-threatening illness. Immunosuppression allows the parasite to multiply rapidly in the small intestine and migrate through the gut to the bloodstream and other organs. This is called disseminated strongyloidiasis (DS) or hyperinfection syndrome (HS), which has a mortality rate of 85–100% from overwhelming sepsis [9]. Common conditions that cause adequate immunosuppression include HTLV-1 infection, malignancy, and exogenous corticosteroid administration [10].

While researchers have been able to shed light on the acute health effects of strongyloidiasis, the long-term consequences of this infection have not yet been fully identified. One of the main hypothesised chronic effects of strongyloidiasis is malnutrition; however, there is insufficient evidence to be certain. Milner et al. have postulated a model by which malabsorption occurs in S. stercoralis-infected patients, where the infection causes oedema and inflammation of the small intestine walls and prevents nutrient uptake [11]. While this is an old study that has struggled to be replicated in similar projects, a theoretical mechanism of malabsorption exists for S. strongyloides, suggesting that the parasite may well lead to malnutrition [12]. If this is the case, chronic strongyloidiasis has a direct clinical relevance to particular sub-groups of society that are most susceptible to harm from malnutrition, such as pregnant women, infants, and children.

Pregnant women are most likely to be affected by strongyloidiasis through two mechanisms: acute severe infection due to immunosuppression, or chronic nutritional deficiencies. Physiological changes during pregnancy cause a level of immunosuppression in the mother, placing her at an increased risk of HS or DS [13,14]. While pregnancy alone has not been observed to cause severe strongyloidiasis, corticosteroids are often administered to women when clinicians suspect a preterm delivery, and this combined effect may immunosuppress the mothers sufficiently to cause severe infection [15]. Some parasitic infections have also been known to cause anaemia during pregnancy, and theoretically S. stercoralis may do the same [16,17].

When looking at the risks to pregnant women, the risks to their unborn fetuses must also be considered. The offspring of infected mothers may be placed at an increased risk of harm from the effects of maternal malnutrition. Multiple studies have researched whether maternal helminth infections are a risk factor for poor pregnancy outcomes, such as intra-uterine growth restriction (IUGR) or low birth weight (LBW). While there is evidence to suggest that this may be the case, it remains unsubstantiated [18–21]. Helminth genera such as Ascaris or Ancylostoma tend to be the focus of such studies; thus there is insufficient literature to demonstrate whether strongyloides does or does not contribute to LBW as well. This is an important gap in knowledge, because if strongyloidiasis does in fact lead to LBW, this means that clinicians are not appropriately screening and treating populations in endemic areas.

Children more generally may also be affected if they become chronically infected during their childhood. Chronic diseases in childhood that produce poor growth are a particular public health concern due to the long term multifactorial consequences they have on individuals and society [22,23]. If strongyloides does cause malabsorption, this will affect the growth and development of children and leave them at an increased risk of poor health outcomes later in life. Insufficient literature is available to determine whether this is the case.

As an NTD, there is a lack of adequate research analysing the effects of strongyloides. Very few studies mention the specific consequences for pregnant women and children, and no systematic reviews have been performed studying the chronic health effects of strongyloidiasis. Those studies that do discuss chronic harm present enough theoretical and observational evidence to hypothesise that there are major health impacts on these sub-groups of the population, justifying the need for a more expansive review of the literature. This review aims to systematically summarise current evidence on the long-term effects that chronic strongyloidiasis has on pregnant women, their offspring, and infected children in general. By doing so, we hope to determine whether these sub-groups are at a potentially higher risk of harm than the rest of the population and highlight current gaps in research.
2. Materials and Methods

This systematic literature review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A) [24]. The review focuses on primary studies that measured the health outcomes of strongyloides infections in pregnant women, the offspring of infected women, and children who were chronically infected during their childhood. The review has been structured according to the ‘Narrative Synthesis’ format described by Mays et al., for ease of reading and in order to easily draw conclusions between studies with different objectives and designs [25]. The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42017069403). Specific questions this review attempts to answer include: what are the current acute and chronic health effects that strongyloidiasis poses to these cohorts, and, what gaps remain in the literature studying chronic strongyloidiasis?

2.1. Search Strategy

The search strategy was based on the database sources of Medline, PubMed, CINAHL, Web of Science, Informit, The Cochrane Collaboration, Scopus, and Google Scholar. A subsequent snowball search of the reference lists of included full text articles was conducted to find further relevant sources. References were stored using EndNote X8™.

The search strategy was centred around six key concepts highlighted in Table 1: ‘strongyloidiasis’, ‘severe disease’, ‘pregnancy’, ‘infant’, ‘immune status’, and ‘eosinophilia’. ‘Severe disease’ was defined as any disease classified in the article as disseminated strongyloidiasis (DS) or hyperinfection syndrome (HS). Pregnancy included the presence of a live fetus at any week of gestation. ‘Immune status’ was used to find references to immunosuppressed populations in which strongyloidiasis may occur, such as HIV or HTLV1-infected cohorts.

| #  | Concept            | Key Words                                    |
|----|--------------------|----------------------------------------------|
| 1  | Strongyloidiasis   | Strongyl * OR Anguillulose                   |
| 2  | Severity of disease| Disseminat * OR Hyperinfect * OR Severe OR Fatal OR Mortality OR Morbidity OR Death * |
| 3  | Pregnancy          | Pregnan * OR Mother * OR Matern * OR Antenat * OR Natal OR Perinat * |
| 4  | Infant             | Neonat * OR Newborn OR Infant * OR Baby * OR Fetus * OR Foetus * OR Fetal OR Preterm OR Child OR Prematur * OR Low Birth Weight OR LBW OR Birth Weight OR Intrauterine Growth Restriction OR IUGR OR FGR OR SGA |
| 5  | Immune status      | Immunocompromised OR Tumour OR Cancer OR Haematolog * OR Lymphom * OR Leukaem * OR Neoplas * OR Malignan * OR HIV OR HTLV1 OR Rheumat * OR Diabet * OR Transplant * OR Steroid * OR Corticosteroid * OR Immunosuppress * OR Glucocorticoid * OR Sepsis |
| 6  | Eosinophilia       | Eosin *                                      |

*keywords were truncated with asterisks added, to locate all forms of the word during the literature search.

Synonyms were drafted with the help of other strongyloidiasis-related literature reviews [6,26,27]. Search terms were modified to fit with the search requirements of each database used, including the use of MeSH terms for PubMed. Literature searching commenced on 26 July 2017 and was completed on 9 August 2017. The full search strategy outlining the combinations of terms used is depicted in Table 2.
Table 2. Combinations of key words used in search strategy.

| Number Search | Combination       |
|---------------|------------------|
| 1.            | 1 + 3            |
| 2.            | 1 + 6            |
| 3.            | 1 + 2 + 3        |
| 4.            | 1 + 2 + 6        |
| 5.            | 1 + 3 + 4        |
| 6.            | 1 + 3 + 5        |
| 7.            | 1 + 3 + 6        |
| 8.            | 1 + 4 + 6        |
| 9.            | 1 + 5 + 6        |

2.2. Data Collection and Analysis

Titles and then abstracts were screened for potential inclusion. The full texts were then read to determine their eligibility according to the search criteria. If the full text could not be found, attempts were made to contact the authors or other institutions to access a full text. Articles that met the criteria were included for analysis.

A standardised spreadsheet was used to extract data from the full text articles. Data items obtained included study date, sample size, country, funding sources, ethics approval, characteristics of participants, outcomes measured, method of testing for *S. stercoralis*, statistical analysis performed, prevalence of strongyloidiasis, eosinophilia, limitations or confounding factors, and results of outcomes measured. Thematic analysis involving the simple pooling of data items was performed. Included studies and their data points were presented in both individual and aggregated tables. Due to the articles being primarily observational studies with a heterogeneous range of outcomes studied, meta-analysis was not performed.

2.3. Inclusion Criteria

We included all quantitative studies that tested for *Strongyloides* infections in cohorts of pregnant women, newborns, or children aged 0 to 18 years of age. If the study cohort focused on children, articles were only included if they measured the long-term effects on participants. Articles were included regardless of what outcomes they measured, such as haemoglobin (Hb) levels, neurocognitive function, or anthropometry. Types of research that were included in this review consisted of randomised control trials, observational studies, and individual case reports. Case reports were included due to the limited results that we found in our scoping searches prior to the formal literature search. By including case reports on top of the more rigorous primary literature, we can present a full landscape of current studies of strongyloidiasis in pregnant women and children.

2.4. Exclusion Criteria

Epidemiological studies that only commented on risk factors for infection (rather than outcomes) were excluded. Animal studies were excluded as no studies specifically looking at strongyloidiasis in pregnant animals were identified. Conference proceedings, poster presentations, and abstracts without a full text were also excluded. No language restrictions or date ranges were placed on included texts.

We hypothesised that there would be very little literature discussing strongyloidiasis in pregnant women and their children, and that many of the studies may have suboptimal methodological quality. As such, we did not exclude studies based on their methodology or statistical analysis used, as if they were found to be of generally poor quality, this would be an important limitation of current research to discuss.
2.5. Methodological Quality

A quality assessment of the observational studies was conducted according to a scale specifically generated for this review (Table 3). The scale is a modification of previously validated tools and used criteria from the Quality Appraisal for Cadaveric Studies (QUACS) scale first used by Smith et al., the Newcastle-Ottawa Scale (NOS), and an independent scale used in a similar systematic literature review [28–30]. QUACS and NOS have been validated as accurate tools to use in observational studies; however, specific items were added to the scale to make it more applicable for assessing the studies included in this review [31]. Due to the heterogeneous nature of methodologies and results used, we refrained from providing a score to assess and compare quality.

**Table 3. Quality assessment tool used for observational studies.**

|                                      | Low Risk                                                                 | Medium Risk                                                                 | High Risk                                                                 |
|--------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Objective stated                     | Aims and objectives fully described with reasons for why they are important | Aims and objectives described, no reasons given for having these aims        | Aims and objectives not fully described                                    |
| Ethics and funding                   | Mentioned, no conflicts                                                  | Mentioned, potential conflicts of interest                                   | Not mentioned or conflicts of interest                                      |
| Methods described                    | Methods discussed and are reliable                                       | Methods discussed, but may not be reliable                                  | Methods not fully discussed                                                |
| Details context of group             | Participant characteristics outlined with discussion of how an accurate sample was ensured | Participant characteristics outlined                                         | Participant characteristics not fully outlined                              |
| Inclusion criteria, exclusion criteria, sample size | Fully described with reasons given                                      | Fully described                                                             | Not adequately described                                                   |
| Education of researchers             | Education given, researchers have appropriate experience or qualifications | Education given, experience or qualifications not mentioned                 | Education and experience is not discussed                                  |
| Methodological bias discussed and addressed | Efforts made to identify and solve potential bias                        | Mention of potential bias in methodology                                     | No mention of bias in methodology                                           |
| More than one researcher             | More than one researcher                                                  | N/A                                                                        | Only one researcher                                                        |
| Statistical analysis appropriate     | Multivariate logistic regression is used                                 | Chi square analysis is used                                                 | Any other form of analysis is used                                         |
| Results presented thoroughly         | Results fully and accurately described                                   | Only partial results given                                                  | Important results omitted or not thoroughly described                       |
| Study discussed in context           | Results analysed according to other studies                              | Results are analysed, some mention of current context                       | Results analysed with no mention to other research                         |
| Clinical implications of results     | Direct clinical application of results is discussed                       | Mention of clinical relevance is made                                        | No mention of clinical implications of results                             |
| Limitations and confounding factors  | Study discussed limitations and confounding factors comprehensively       | Some discussion of limitations and confounding factors                       | No discussion of limitations or confounding factors                        |

N/A: not applicable.

Case series were assessed for quality according to the Joanna Briggs Institute Critical Appraisal Tool: Checklist for Case Reports [32]. The risk of bias evaluations was not used to exclude studies from data synthesis but rather would be utilised to comment on the current gaps in literature and accuracy of results.
3. Results

Database and reference list searching returned 1666 unique results, of which 94 were considered eligible for full-text review. The full texts of 29 sources could not be found, even after attempts were made to contact authors, libraries, and institutions to access a copy. These studies were decades old, focused on other parasites, and from the citation information available did not indicate that they would add further use to this review or significantly change the conclusions. This left 65 full-text articles that were read in full. Based on our inclusion and exclusion criteria, 45 articles were then excluded. Thirty-nine full texts were excluded as they were either found to be irrelevant or were solely epidemiological studies and did not measure health outcomes of their participants. Six studies were found to be review articles and were subsequently excluded. This left a total of 20 studies for inclusion.

Sixteen articles were sourced from electronic library databases, while the remaining four studies were individually added from the Google Scholar search; no further articles were added after reviewing the reference lists of included full-texts. Sixteen studies were original research papers while four articles were individual case reports that discussed Strongyloides in pregnant women. Countries in which studies were performed included Australia (1), France (1), Ghana (2), Guatemala (1), India (1), Kenya (1), Nigeria (1), Papua New Guinea (3), Peru (2), Tanzania (1), Thailand (2), Uganda (2), Unites States of America (USA, 2) and Venezuela (1). Publication dates of the articles ranged from 1989 until 2015. The outcomes of the search strategy are summarised in Appendix B. For the purpose of clarity, the research papers will be discussed separately to the case studies.

3.1. Study Characteristics

Participant demographics included pregnant women (3), pregnant women and their newborn children (5), or only infected children (8). Participants were mostly from low socio-economic environments, and hygiene was typically stated as poor in the studies. Only one study focused specifically on S. stercoralis infections, and two studies focused on S. fuelleborni. The majority of studies either surveyed all helminth infections in their cohorts, or their main focus was on other helminths, malaria, or HIV, and happened to include data on strongyloidiasis. The study settings included in-hospital environments (3), community settings (10), or antenatal and postnatal clinics (3) (Table 4).

3.2. Quality Assessment

Overall, the methodological rigour of the literature was of a low quality. With regard to the prospective studies, 16 were cohort studies while only one was a case-control study; there were no randomised controlled trials included. The studies were found to vary widely in their study designs, attempts to control bias, and outcomes measured (Appendix C, Figure A3).

Nine studies used logistic regression, while five studies use chi-square analysis. The majority of studies did not consider or report potential bias being present in their studies and took limited steps to prevent this from affecting their results. Many studies did not adequately discuss their inclusion and exclusion criteria, sample sizes, or the involvement of researchers in data collection. The cohorts were often arbitrarily chosen and not adequately matched. Many of the studies were quoted to be using data from other larger trials without discussing any potential bias in these results. The majority of studies only reported data selectively and did not specify the non-significant results.

Case reports were overall of a high quality and comprehensively discussed the clinical relevance of their patients (Appendix C, Figure A4).

3.3. Risk of Bias of Included Studies

Generally, the literature did not appropriately comment on potential limitations or confounding factors to their research. Some commonly mentioned limitations amongst studies included small sample sizes, small prevalence data of S. stercoralis, inappropriate testing methods, and inability to follow-up with included participants.
### Table 4. Study Characteristics.

| Author, Year, Country | Study Design | Participant Characteristics | Sample Size | Length of Review | Setting | Prevalence |
|-----------------------|--------------|-----------------------------|-------------|------------------|---------|------------|
| Baidoo et al., (2010), Ghana [33] | Prospective observational cohort study | Pregnant women | 108 | 12 months | Community | 2% |
| Barnish et al., (1989), Papua New Guinea [34] | Prospective observational cohort study | Children <5 years | 12 | NR | Community | 63% |
| Cabada et al., (2014), Peru [35] | Prospective observational cohort study | Amazonian clan members, all ages | 215 | NR | Community | 6% |
| Mangklabruks et al., (2012), Thailand [36] | Prospective observational cohort study | Newborns followed from antenatal clinic visits | 2184 | 1 year 9 months | Antenatal and postnatal clinics | 0.8% |
| Dada-Adegbola et al., (2004), Nigeria [37] | Prospective observational cohort study | Children <5 years with diarrhoea | 227 | NR | Hospital | 5.3% |
| Dreyfuss et al., (2001), Tanzania [38] | Prospective observational cohort study | HIV-infected pregnant women and their newborns | 822 | NR | Antenatal and postnatal clinics | 1.78% |
| Egger et al., (1990), Thailand [39] | Prospective observational cohort study | Children 3-8 years | 343 | NR | Community | 25.4% |
| Herrera et al., (2006), Peru [40] | Prospective observational case-control study | Community members <20 years | 100 | 1 month | Community | NR |
| King et al., (2004), Papua New Guinea [41] | Prospective observational cohort study | Children <5 years | 179 | 4 months | Community | 27% |
| LaBeaud et al., (2015), Kenya [42] | Prospective observational cohort study | Mothers and their infants <3 years | 545 | 3 years | Community | NR |
| Muhangi et al., (2007), Uganda [43] | Prospective observational cohort study | Pregnant women | 2507 | 1 year 7 months | Hospital | 12.3% |
| Nampijja et al., (2012), Uganda [44] | Prospective observational cohort study | Mothers and their infants <15 months | 983 | 2 years | Antenatal and postnatal clinics | 13% |
| Phuanukoornnon et al., (2013), Papua New Guinea [45] | Prospective observational cohort study | Pregnant women | 201 | 1 year 5 months | Community | 3% |
| Verhagen et al., (2013), Venezuela [46] | Prospective observational cohort study | Children 4-17 years | 390 | 1 year 6 months | Community | 7.9% |
| Villar et al., (1989), Guatemala [47] | Prospective observational cohort study | Mothers and their newborns | 14,914 | 1 year 9 months | Community | 0.4% |
| Yatich et al., (2010), Ghana [48] | Prospective observational cohort study | Mothers and their newborns | 746 | 2 months | Hospital | 3.9% |

NR: not reported.
3.4. Prevalence

The prevalence of *S. stercoralis* in the studies was typically low, with a mean prevalence of 12.3% and the median prevalence being 6%. Studies with mixed urban and rural cohorts found that the prevalence of strongyloidiasis was higher in participants from rural areas. A few studies noted that their prevalence data was unreliable due to using suboptimal testing methods that have been proven to be inaccurate for detecting *S. stercoralis* [6].

3.5. Method of Testing

All the studies included in this review used various methods of stool-sample analysis to determine the rates of *S. stercoralis* infections in their cohorts. Methods included the Baermann (3 studies), Kato-Katz (4), Ritchie (1), formol-ether concentration (2), simple smear technique (1), volume dilution method (1), or were unspecified (4). No studies utilised serological testing. Single samples with limited follow-up were used, rather than the serial testing of multiple specimens.

3.6. Effects on LBW

Four studies measured the effect that *S. stercoralis* infection in pregnant women had on the birth weight of their offspring [36,38,47,48]. Two studies, one in Thailand and one in Tanzanian HIV-infected mothers, found odds ratios of 4.93 (95% CI 1.47, 16.50) and 4.23 (95% CI 1.24, 14.41), respectively, that LBW was caused by strongyloidiasis (Table 5) [36,38]. One study in Ghana found an odds ratio of 2.1 (95% CI 0.97, 4.49) for LBW, small for gestational age (SGA), or preterm delivery [48]. The fourth study found a non-significant increased risk of IUGR; the study attributed a low prevalence of strongyloidiasis to the failure to achieve a statistically significant result [47]. IUGR was predominantly seen in malnourished women who had strongyloidiasis, and the study authors hypothesised this as a possible cause rather than the helminth itself. None of the studies measured the length of duration of *S. stercoralis* infection in the pregnant mother, or the intensity of larval output as an indicator of the severity of the infection.

3.7. Anthropometry

Five studies analysed whether there were long term effects of *Strongyloides* infections on the nutrition and growth of infected children (Table 6) [39–42,46]. Three studies found that strongyloidiasis was associated with decreased weight-for-height or weight-for-age z-scores. However, not all of these were statistically significant [39,40,46]. These measurements are more typically used to determine wasting, which is an acute indicator of malnutrition, rather than the more chronic indicator of stunting. One study found a statistically significant relationship between strongyloidiasis and decreased height-for-age z-score (*p* < 0.01), which is used to measure stunting [39]. One study found that at 30 months of age, children with strongyloidiasis had a decreased head circumference (*p* = 0.002); this same study did not find any significant link to other anthropometric measures. One study found no statistically significant relationships between stunting, wasting, and *S. stercoralis* infections, but did note that the intensity of infection was associated with decreased weight-for-age and weight-for-height z-scores, within the *Strongyloides*-infected population (*p* = 0.02, 0.016 respectively) [41]. Another article found that children infected with strongyloidiasis were substantially more likely to suffer from marasmus or kwashiorkor when compared to non-infected children (*p* = 0.001) [40]. The majority of studies also found that polyparasitism was more strongly associated with lower z-scores of all the anthropometric measures when compared to solely *S. stercoralis* infection.
### Table 5. Methodology and outcomes of *Strongyloides* infections.

| Study | Only *S. stercoralis* Is Assessed | Results Are Aggregated | Testing Method for *S. stercoralis* | Statistical Analysis | Results |
|-------|-----------------------------------|------------------------|-----------------------------------|----------------------|---------|
| 33    | No                                | Yes                    | Stool; formol-ether concentration method | Chi-square test | Helminth infections are a predictor of iron-deficiency anaemia in pregnant women |
| 34    | No                                | No                     | Stool; not specified               | Correlation coefficient | Heavy infection predisposes to poor growth |
| 35    | No                                | No                     | Stool; Kato-Katz method            | Chi-square test | High rates of anaemia and malnutrition in children Helminth infections not associated with these outcomes *Strongyloides* was not managed by treatment |
| 36    | No                                | Yes                    | Not specified                      | Multivariate logistic regression | Odds ratio of 4.93 of *Strongyloides*/hookworm infection in pregnancy causing LBW (95% CI 1.47, 16.50) |
| 37    | Yes                               | N/A                    | Stool; formol-ether concentration methods | Logistic regression | Higher rates of malnourished in *Strongyloides*-infected children Malnutrition may increase the risk of contracting *Strongyloides* |
| 38    | No                                | No                     | Stool; Kato-Katz method            | Multivariate logistic regression | Odds ratio of 4.23 for *Strongyloides* causing LBW (95% CI 1.24, 14.41) |
| 39    | No                                | No                     | Stool; simple smear technique      | Chi-square test | Lower mean height-for-age z-score (p < 0.01) |
| 40    | No                                | No                     | Stool; Baermann method             | Multivariate logistic regression | Malnutrition more common in *Strongyloides* infections No relationship between *Strongyloides* and anthropometry |
| 41    | No                                | No                     | Stool; volume dilution method      | Logistic regression | *Strongyloides* associated with decreased weight-for-age z-score (p < 0.05) Not associated with weight-for-height z-score (p < 0.05) |
| 42    | No                                | No                     | Stool; Ritchie method              | Logistic regression | *Strongyloides* at 30 months is associated with decreased head circumference (p = 0.002) |
| 43    | No                                | No                     | Stool; Kato-Katz method            | Logistic regression | No relationship between *Strongyloides* and anaemia |
| 44    | No                                | No                     | Stool; Kato-Katz method            | Logistic regression | Negative impact on language function of infants (p < 0.05) Non-significant impact on gross motor, sociocognition, and self-care |
| 45    | No                                | Yes                    | Stool; not specified               | Chi-square test | No relationship to anaemia |
| 46    | No                                | No                     | Stool; Baermann and Kato-Katz methods | Multivariate logistic regression | No relationship to anaemia |
| 47    | No                                | No                     | Not specified                      | Multivariate logistic regression | Non-significant relationship between weight-for-age and BMI-for-age |
| 48    | No                                | No                     | Stool; Baermann method             | Chi-square and t-test | Increased risk of IUGR Malnourished women with *Strongyloides* most at risk |

N/A: not applicable.
Table 6. Anthropometric changes associated with *S. stercoralis* infections.

| Study | Weight-for-Age $z$-Score | Weight-for-Height $z$-Score | Height-for-Age $z$-Score | Head Circumference $z$-Score |
|-------|--------------------------|-----------------------------|--------------------------|-----------------------------|
| 39    | NR                       | −1.01 ($p = \text{NS}$)     | −2.03 ($p < 0.01$)       | NR                          |
| 40    | Positive association ($p = 0.045$) | NR                       | No association ($p = 0.24 $) | NR                          |
| 41    | No association            | No association              | No association            | NR                          |
| 42    | No association            | No association              | No association            | −1.69 ($p = 0.002$) at 30 months |
| 43    | NR                       | −0.24 ($p = \text{NS}$)     | NR                       | NR                          |

NR: not reported.

Generally, consensus from the studies was that malnutrition either predisposes participants to *S. stercoralis* infections or chronic strongyloidiasis may cause malnutrition. Due to their study designs, firm conclusions could not be made to determine whether strongyloidiasis is a risk factor or consequence of malnutrition. This issue becomes further complicated when considering that strongyloidiasis was seen more commonly in populations of lower socio-economic status, as malnutrition is also more commonly observed in these groups.

3.8. Strongyloidiasis and Anaemia

Five studies measured whether *S. stercoralis* contributed to maternal anaemia [33,35,43,45,46]. One study found that helminth infections were a predictor of iron-deficiency anaemia. However, the helminths were not differentiated in the results so conclusions cannot be made about the effects of *S. stercoralis* [33]. The other four studies found no relationship between strongyloidiasis and anaemia.

3.9. Case Reports

Four case reports were found as part of the literature search that fulfilled our inclusion criteria (Table 7) [49–52]. All four cases describe women who presented at varying stages of gestation with predominantly gastrointestinal or respiratory symptoms. Two cases were classified as HS, one as DS, and one was symptomatic but non-disseminated. Corticosteroids preceded two of the cases, and in both of these cases the patients were found to have either HS or DS. Two women had HTLV-1 co-infections, which has been previously noted as a common occurrence. Two women required ICU admissions, and one patient died from cardiorespiratory arrest secondary to septic shock. Fetal demise also occurred in the patient who passed away [48].

All patients were treated with ivermectin. Of the three women who survived, all underwent spontaneous vaginal births to healthy babies, with no complications. They made a full recovery from the infection, although one mother re-presented a year later, again pregnant and suffering from gastrointestinal symptoms [50]. She was found to have been re-infected with *S. stercoralis*. 
Table 7. Summary of case reports.

| Author, Year, Country | Country of Origin, Gestation | Presenting Complaint | HS or DS? | Corticosteroids Administered | Treatment | Outcome |
|-----------------------|-----------------------------|----------------------|-----------|-----------------------------|-----------|---------|
| Buresch et al., 2015, USA [49] | Haiti, 25 weeks | Chest pain, dyspnoea, copious bilious vomiting | HS | Betamethasone 12 mg, 2 doses 24 h apart | Ivermectin | Septic shock, SIRS, cardiopulmonary arrest, fetal demise |
| Heaton et al., 2002, USA [52] | Ethiopia, 9 weeks | Diarrhoea, epigastric pain, vomiting | None | None | Ivermectin 200 µg/kg | SVB at term, cleared of infection |
| Malézieux-Picard et al., 2016, France [50] | Burkina Faso, 32 weeks | Abdominal pain, anorexia, constipation, weight loss | HS | Betamethasone 12 mg stat | Ivermectin 200 µg/kg/day for 3 days | SVB, recovered from infection |
| Prasad et al., 2016, India [51] | India, 39 weeks | Cough, watery diarrhoea | DS | None | Ivermectin 12 mg | SVB, cleared of infection |

SVB: spontaneous vaginal birth.
4. Discussion

This review aimed to summarise current literature that analysed the long-term health outcomes of strongyloidiasis on pregnant women, their offspring, and children. Our findings suggest that there are enduring consequences for children that are either born to infected mothers, or who are chronically infected early in their development. To our knowledge, this is the first systematic literature review that attempts to determine the possibility of chronic health effects caused by strongyloidiasis in these subgroups.

The small number of studies that investigated the birth outcomes of newborns with infected mothers found that there is an association between strongyloidiasis and LBW. The 95% confidence intervals of these studies were large, despite always showing positive associations with LBW. Research has consistently recognised LBW to have lasting impacts on the morbidity and mortality of these newborns, as per the Barker and Brenner hypotheses [53]. The reliability of strongyloidiasis causing LBW is still questionable, as studies were conducted in developing countries with participants that had a range of other comorbidities (such as HIV). Therefore, further research and analysis of this potential risk factor is required. If strongyloidiasis is confirmed to cause LBW, the infection should be treated like other known risk factors for LBW, and women should receive appropriate prenatal screening and treatment [54].

Studies that measured the anthropometry of infected infants and children generally agreed that strongyloidiasis did result in a negative impact on their growth. Wasting and stunting are long-term detriments to the wellbeing of children, and research has established that they lead to increased medical comorbidities, reduced schooling, and reduced economic productivity [55,56]. The main effects of strongyloidiasis were only seen in the more acute measurement of wasting, rather than the more chronic indicator of stunting, thus the clinical implications of this finding are less certain. However, a study conducted by Richard et al. found that wasting was associated with stunting and the long-term effects that go with this [57]. Therefore, strongyloidiasis is likely to have clinically significant impacts on the health of people infected during childhood. Ivermectin should be used as part of existing community and school-based deworming initiatives in endemic areas, to prevent the enduring consequences of wasting.

The assessment of strongyloidiasis affecting the growth of children is affected by the small number of included articles that commented on these measurements. Studies also did not publish their full results lists, and the differences in cohort characteristics were large. Epidemiologically, the studies were unable to determine if strongyloidiasis was more common in malnourished children or if the disease process itself caused malnutrition. As the studies were cross-sectional, no studies looked at whether children had been chronically infected with strongyloidiasis. In order to confidently conclude that *S. stercoralis* does in fact cause deficiencies in growth and therefore have direct clinical consequences, longitudinal studies of affected participants with larger sample sizes need to be performed.

Several studies noted a range of common epidemiological risk factors which may lead to a greater risk of infants and pregnant women contracting this infection. Absence of footwear, other household members already being infected, and poor sanitation facilities, were all emphasised in the studies as potential risk factors. This poses another challenge to public health strategies, as newborns can quickly become chronically infested from their mothers or family members. Even if strongyloidiasis does not cause LBW, maternal infection can still cause chronic health effects due to the high likelihood of passing on their infection early in childhood and causing malnutrition, wasting or stunting. Interventions targeting water, sanitation, and hygiene (WASH) may provide a solution to reducing these epidemiological risk factors and therefore the long-term consequences of strongyloidiasis [58].

Based on the review findings, anaemia should not be considered a potential complication of *S. stercoralis* infections. This is in contrast to other helminths such as hookworm, which have been more strongly linked with anaemia [59]. Studies that have observed the clinical manifestations of strongyloidiasis in different cohorts have produced conflicting results regarding anaemia [60,61]. The primary reason why we are still not sure whether *S. stercoralis* causes anaemia is because both are
typically common in under-nourished, socio-economically poorer populations with increased health comorbidities. This makes the task of attributing anaemia to the helminth difficult.

There is a paucity in literature looking at the effects of *S. stercoralis* infection on pregnant women, their offspring, and infected children. The only literature that could be found that mentions pregnant women with severe infection were case studies; no prospective studies could be found in which pregnancy was researched as a potential risk factor of HS or DS. Likewise, very little information currently exists to determine whether *S. stercoralis* infection in the mother is an independent risk factor for LBW, SGA, IUGR, or preterm delivery. As there were so few studies found analysing these variables, this may suggest a publication bias is present which has inflated the health effects strongyloidiasis has on these populations.

Although only a few case reports exist that discuss strongyloidiasis in pregnancy, the ones found in this review showed that this infection can cause severe or ultimately fatal complications. Pregnant women are already immunosuppressed and thus may be at a higher risk of hyperinfection syndrome. Clinicians must currently rely on individual cases for information on the possible disease course of strongyloidiasis or look elsewhere to different population groups. Corticosteroids preceded 50% of the onset of HS, although the sample was small. In areas endemic to *S. stercoralis*, women giving preterm birth or who are immunosuppressed are at risk of these severe complications and should be screened accordingly.

There is reason to believe that the prevalence and therefore the health effects of strongyloidiasis is underestimated in the current literature. The majority of studies only included *S. stercoralis* as one of many parasites tested. As the researchers were not directly focusing on strongyloidiasis they accordingly did not use accurate diagnostic tests and therefore are likely to have missed a significant amount of *S. stercoralis* infections in their participants. Even amongst stool samples, the gold standard of seven serial samples was not performed [1]. This may have had the potential to understate the longitudinal consequences strongyloidiasis had on children and thereby prevented studies from achieving statistical significance. This failure to achieve significance and the substantially low prevalence data compared to other helminths may have resulted in unpublished data, creating a relative publication bias in the literature reviewed. Healthcare providers would benefit from more accurate prevalence data in order to appropriately manage these subgroups. Therefore, the convenient and reliable serological tests should be used in further studies on strongyloidiasis.

If strongyloidiasis does indeed lead to adverse health effects in infants, this has direct clinical implications for endemic areas. This review strengthens arguments for increased screening and treatment of pregnant women to confer the best possible outcome for their children. Ivermectin has been proven to be safe in pregnancy, despite not currently being used due to its assigned pregnancy category of B3 [62]. The clinicians in all four case reports used ivermectin and no complications were observed. It is the opinion of the authors that there is enough favourable evidence to support the use of ivermectin in pregnancy, particularly given the significance of the consequences to mothers and children. Health practitioners in endemic areas would benefit from further clarification of whether this drug is appropriate for use in pregnant women.

The findings outlined in this review need to be considered with caution, as only a small number of studies have currently looked at these effects and their methodological quality may be considered suboptimal. While some studies did achieve statistical significance in their findings, they often occurred in small samples, in participants with comorbidities such as HIV or malnutrition, and in countries in developing nations; thus, their findings cannot be generalised.

**Limitations**

A number of limitations to this review have been identified and must be taken into consideration when analysing the findings. Studies reviewed used varying methods of statistical analysis, which were presented and compared despite some results not being statistically significant or insufficiently powered. Many studies were conducted decades ago in vastly different contexts, using less accurate
testing methods. It was unfortunate that some studies aggregated the results of *S. stercoralis* with other helminths such as hookworm; these were still included in the review. A significant proportion of our included full-texts also could not be found. Meta-analysis could not be performed and thus only simple pooling of results was possible. Due to the marked variation in the outcomes assessed by different studies, the findings were compared between cohorts that varied dramatically in their characteristics. Because of these limitations, a level of bias in the findings was unavoidable, despite taking steps to ensure transparency and academic rigour.

5. Conclusions

In conclusion, current research is suggestive that maternal strongyloidiasis is a risk factor for LBW. However, a lack of literature and sub-optimal study designs prevents this from being a certainty. Chronic infection in childhood is most strongly associated with wasting and may potentially lead to stunting. Due to similar issues, current research is unable to ascertain whether strongyloidiasis leads to malnutrition or is just more commonly found in the malnourished. The strongest conclusion gleaned from this literature review was that the prevalence of strongyloidiasis was very likely underestimated, due to the methods of testing and lack of focus on this specific helminth in the study designs. In order to truly determine whether pregnant women, their offspring, and infected children are in fact susceptible sub-groups of the population, further longitudinal research utilising modern serological techniques and control groups is required.

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**Conflicts of Interest:** The authors declare no conflict of interest.
Appendix A

| Section/topic                  | #  | Checklist item                                                                 | Reported on page # |
|-------------------------------|----|---------------------------------------------------------------------------------|-------------------|
| **TITLE**                     |    |                                                                                  |                   |
| Title                         | 1  | Identify the report as a systematic review, meta-analysis, or both.              | 1                 |
| **ABSTRACT**                  |    |                                                                                  |                   |
| Structured summary            | 2  | Provide a structured summary including, as applicable: background, objectives,  | 1                 |
|                               |    | data sources, study eligibility criteria, participants, and interventions, study |                   |
|                               |    | appraisal and synthesis methods; results; limitations; conclusions and           |                   |
|                               |    | implications of key findings; systematic review registration number.             |                   |
| **INTRODUCTION**              |    |                                                                                  |                   |
| Rationale                     | 3  | Describe the rationale for the review in the context of what is already known.   | 2                 |
| Objectives                    | 4  | Provide an explicit statement of questions being addressed with reference to    | 3                 |
|                               |    | participants, interventions, comparisons, outcomes, and study design (PICOS).    |                   |
| **METHODS**                   |    |                                                                                  |                   |
| Protocol and registration     | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g.,    | 3                 |
|                               |    | Web address), and, if available, provide registration information including      |                   |
|                               |    | registration number.                                                            |                   |
| Eligibility criteria          | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report     | 3                 |
|                               |    | characteristics (e.g., years considered, language, publication status) used as  |                   |
|                               |    | criteria for eligibility, giving rationale.                                     |                   |
| Information sources           | 7  | Describe all information sources (e.g., databases with dates of coverage,      | 3                 |
|                               |    | contact with study authors to identify additional studies) in the search and    |                   |
|                               |    | date last searched.                                                             |                   |
| Search                        | 8  | Present full electronic search strategy for at least one database, including any | 4                 |
|                               |    | limits used, such that it could be repeated.                                    |                   |
| Study selection               | 9  | State the process for selecting studies (i.e., screening, eligibility, included  | 4                 |
|                               |    | in systematic review, and, if applicable, included in the meta-analysis).       |                   |
| Data collection process       | 10 | Describe method of data extraction from reports (e.g., piloted forms,          | 4                 |
|                               |    | independently, in duplicate) and any processes for obtaining and confirming     |                   |
|                               |    | data from investigators.                                                        |                   |
| Data items                    | 11 | List and define all variables for which data were sought (e.g., PICOS,         | 4                 |
|                               |    | funding sources) and any assumptions and simplifications made.                  |                   |
| Risk of bias in individual    | 12 | Describe methods used for assessing risk of bias of individual studies (including| 5                 |
| studies                       |    | specification of whether this was done at the study or outcome level), and how  |                   |
|                               |    | this information is to be used in any data synthesis.                          |                   |
| Summary measures              | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | 4                 |
| Synthesis of results          | 14 | Describe the methods of handling data and combining results of studies, if done, | 4                 |
|                               |    | including measures of consistency (e.g., P< for each meta-analysis.              |                   |
| Section/topic                          | # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|--------------------------------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies          | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                                                                                                                                                 | 5                 |
| Additional analyses                  | 16| Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                                                                                                                                                     | N/A               |
| **RESULTS**                          |   |                                                                                                                                                                                                                                                                                                                                                                                                          |                   |
| Study selection                      | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                                                                                                                                                 | 6                 |
| Study characteristics                | 18| For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                                                                                                                                                                                                                     | 9                 |
| Risk of bias within studies          | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                                                                                                                                                         | 8                 |
| Results of individual studies        | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.                                                                                                                                                    | 6                 |
| Synthesis of results                 | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency (see Item 15).                                                                                                                                                                                                                                    | N/A               |
| Risk of bias across studies          | 22| Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                                                                                                                                              | 8                 |
| Additional analysis                  | 23| Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                                                                                                                                                                  | N/A               |
| **DISCUSSION**                      |   |                                                                                                                                                                                                                                                                                                                                                                                                          |                   |
| Summary of evidence                  | 24| Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                                                                                                                                                                      | 11                |
| Limitations                          | 25| Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                                                                                                                                                               | 13                |
| Conclusions                          | 26| Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                                                                                                                                                                               | 14                |
| **FUNDING**                          |   |                                                                                                                                                                                                                                                                                                                                                                                                          |                   |
| Funding                              | 27| Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                                                                                                                                                        | 14                |

**Figure A1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.
Appendix B

Figure A2. PRISMA flow diagram.

Appendix C

|   | Objective stated | Ethics and funding | Methods described | Sample, setting, or intervention | Inclusion criteria | Exclusion criteria | Sample size | Statistical analysis | Results presented | Study discussed in context | Clinical implications of results | Limitations and confounding factors |
|---|------------------|-------------------|-------------------|----------------------------------|-------------------|-------------------|-------------|---------------------|------------------|--------------------------|-----------------------------|---------------------------------|
| 33 | M                | M                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 34 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 35 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 36 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 37 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 38 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 39 | M                | M                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 40 | L                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 41 | H                | H                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 42 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 43 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 44 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 45 | H                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 46 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 47 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |
| 48 | M                | L                 | M                 | M                                | M                 | M                 | M          | M                   | M                | M                        | M                          | M                               |

Figure A3. Quality assessment scale.
Figure A4. Quality assessment according to JBI Critical Appraisal Tool: Checklist for Case Reports.

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