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Optimum nutrition of the pregnant ewe:
A meta-analytic approach

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Abstract

Formal systematic review guidelines and meta-analytic methods were used in the present study to achieve three main objectives. Firstly, literature on the effect of ewe nutrition during pregnancy on fetal and postnatal lamb growth was reviewed and effect sizes estimated for fetuses/lambs at three stages of their life: 1) late gestation fetal weight (LGFW), 2) lamb birth weight (BW) and 3) weaning weight (WW). Secondly, the contribution of experimental factors responsible for variation in study results was determined. Thirdly, a field trial was conducted to increase understanding in an area identified by the meta-analyses as requiring further experimentation. Overall, early- and mid-pregnancy undernutrition had no significant effect on LGFW ($\beta_{\text{[Early-pregnancy]}} = -0.0007$, 95% Highest posterior density (HPD) = -0.26 to 0.28; $\beta_{\text{[Mid-pregnancy]}} = -0.07$, 95% HPD = -0.27 to 0.16), BW ($\beta_{\text{[Early-pregnancy]}} = 0.01$, 95% HPD = -0.36 to 0.34; $\beta_{\text{[Mid-pregnancy]}} = -0.02$, 95% HPD = -0.36 to 0.33) and WW ($\beta_{\text{[first 100 days of pregnancy]}} = -0.008$, 95% HPD = -0.42 to 0.18), suggesting that short to moderate periods of undernutrition in these stages are tolerated by ewes with limited impact on their offspring, when nutrition is re-established to pregnancy maintenance (PM) or above levels during late-pregnancy. Late-pregnancy undernutrition can significantly decrease LGFW and BW by up to 1.15 kg at birth, with residual effects at weaning resulting in weaned lambs that are up to 18% lighter than their control counterparts and thus, should be avoided. The present study also considered the effect of maternal above PM feeding on LGFW, BW and WW. The combined effects across these studies were variable, as few experiments investigated above PM feeding at each stage of pregnancy, and thus it was not possible to draw definitive conclusions. A field

experiment was undertaken to determine the effects of *ad-libitum* (AL) feeding at various stages of pregnancy and for differing lengths of time on twin lamb BW and WW. Results showed that providing ewes with AL feeding significantly ($p < 0.05$) increased their live weight and BCS, but did not increase ($p > 0.05$) the BW or WW of their lambs relative to their control counterparts. This study also suggested that AL feeding during late-pregnancy may have negative consequences to the survival of twin lambs and requires further examination. Thus, AL feeding is not justified as a management tool to increase twin lamb BW and WW, when nutrition is adequate during lactation. The present study represents the first meta-analytic approach examining the effect of changes in the ewe nutrition during pregnancy on the growth of offspring at various developmental stages. Given the complex interrelationship between nutrition of the pregnant ewe, her reproductive success, fetal growth and development, and offspring post-natal performance, no single study can provide a definitive understanding of responses to a particular treatment and there is value in combining available experimental evidence to elucidate a more global picture. A meta-analytic approach can find trends in combined data that would otherwise be overlooked using traditional review methods and can also identify gaps in current knowledge.

Key words: meta-analysis, sheep, pregnancy, undernutrition, *ad-libitum*.

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Chapter 1: Literature review

1.1 Preamble

Animal Science, in particular animal nutrition, has made considerable progress over the past 25 years (Makkar, 2016) in regards to defining animal nutrient needs and physiological interactions. In animal agriculture and biomedical sciences, an increasing body of evidence now exists showing that the nutrition of the pregnant ewe exerts a profound influence on offspring growth and development (see reviews by Wu et al. 2007; McMillen et al. 2009; Caton and Hess, 2010; Kenyon and Blair, 2014; Rooke et al. 2014; Mossa et al. 2015; Bell and Greenwood, 2016). This is important from an agricultural standpoint because understanding the factors that can influence the growth trajectory of the young animal is of great practical and economic importance to the farmer.

Primary research investigating the effect of changes in the ewe nutrition during pregnancy on offspring outcomes are characterised by a diversity of experimental factors that could have a bearing on the magnitude of any observed effects. In general, all these factors can be divided into three groups: firstly, study-related factors, which include the type, length, timing and severity of the nutritional manipulation and the nutritional level provided after the intervention period; secondly, maternal-related factors, which include breed, age, live weight and condition score, and; thirdly, offspring-related factors, which include gestation length, genotype, litter size and sex (Harding and Johnston, 1995; Greenwood and Bell, 2003; Luther et al. 2005; Kenyon and Blair, 2014; Bell and Greenwood, 2016). Therefore, it is not surprising that fetal and lamb weight responses across studies can often result in highly variable study outcomes and conclusions.

The complex interrelationships between all these factors make comparing individual studies difficult. Thus, making it challenging to summarise the available evidence by simply contrasting studies in a narrative manner. Indeed, whilst many of these experimental factors have been acknowledged in many narrative reviews (Harding 2001; Greenwood and Bell 2003; McMillen and Robinson 2005; Wu et al. 2006; Greenwood and Thompson, 2007; Caton and Hess, 2010; Kenyon and Blair, 2014; Rooke et al. 2015), the contribution of each of these factors to the variation in observed results can only be hypothesised as effects have not been quantified. Agricultural scientists need a quantitative estimation of the effects across experiments to determine whether changes in offspring weight at different developmental stages are economically important for agricultural production, and how these changes can be affected by other experimental factors. Meta-analysis is a powerful statistical tool used to quantitatively summarize study outcomes and to understand the factors that contribute to the variability across studies (Gerstner et al. 2017). Although it was originally developed to summarize human studies in the social and medical sciences, it is now routinely used in other biological sciences like ecology, physiology and evolutionary biology, where non-human species are the main focus (Nakagawa et al. 2017). Yet, in the animal sciences, the use of meta-analysis as a tool to synthesise previously published studies is more sporadic and perhaps less known. It is therefore relevant to put into perspective the advantages and disadvantages of meta-analysis in relation to other review methods, as well as to provide an appraisal of the statistical techniques used in research areas where meta-analysis is routinely employed and developed

1.2 Narrative, systematic and meta-analytic reviews

Every year, more than 10,000 leading journals are published around the world (Thomson Reuters, 2013), suggesting an ever-increasing scientific output. As information continues to expand, scientists must rely on integrative reviews in order to stay up-to-date with the new scientific evidence (Rapple, 2011). Traditionally, there are three approaches when conducting an integrative literature review: (i) narrative reviews, (ii) qualitative systematic reviews and (iii) quantitative systematic reviews or meta-analysis (Green et al. 2006). The purpose of all these integrative review methods is to find common ideas and concepts from the reviewed material (Pautasso, 2013); however, they differ in methodology and scope (Collins and Fauser, 2005).

Narrative reviews are comprehensive summaries of previously published information and tend to cover a broad range of issues within a given topic. Commonly, narrative reviews provide the reader with a list of studies from which the reviewer takes many pieces of information to tie together into a narrative, readable format (Green et al. 2001). Despite their valuable input as educational articles bringing scientists up to date with the new knowledge, narrative reviews have been criticised on two main points. First, a typical narrative review does not necessarily follow a specific methodology for how it gathers its evidence (Collins and Fauser, 2004) and when they do, the details are more often than not unavailable to the reader (Hunt, 1997). The lack of precision and reproducibility of the methodological approach in narrative reviews can influence the way results are interpreted, mostly because they are susceptible to the subjective judgement, preferences and biases of a particular reviewer (Hunt, 1997). Failure to systematically search for literature and consequently for explanations of the variation in study outcomes often leads to an

incomplete, biased and irreproducible collection of primary studies (Green et al. 2006; Borenstein et al. 2009). The absence of an explicit “review methodology” makes it difficult to make judgment about the author’s choices and methods.

A second argument against narrative reviews is the use of a procedure often referred to as “vote-counting”. Traditional vote-counting methodology makes use of the outcome of the test of significance (i.e. p -values) in a series of similar studies to determine a conclusion about the overall experimental effect (Light and Smith, 1971). A detailed discussion as to the advantages and disadvantages of using p -values to draw conclusions about a series of experiments is beyond the scope of this literature review, but has been covered by other authors (Hedges and Olkin, 1985; Nakagawa and Cuthill, 2007; Cooper et al. 2009). Briefly, p -values are heavily influenced by sample size and cannot be compared across studies. In addition, p -values do not measure the magnitude of an effect since they represent the answer to a dichotomous question: “is the observed effect due to chance or not?”, rather than an open-ended one: “how strong is the pattern of the data?” (Cooper et al. 2009; Harrison, 2011). A reliance solely on p -values may mean that other relationships are overlooked (Cumming, 2012). For example, vote-counting disregards the magnitude of any treatment effect, and Hedges and Olkin (1980, 1985) showed that this procedure is strongly biased towards the conclusion that a given treatment has no effect. A simple example is to determine which of the following treatment effects is the largest, assuming that three studies have treatment and control groups with equal size (Wang and Bushman, 1999):

a) $t(256) = 4.0, p < 0.001$

b) $t(64) = 2.0, p < 0.05$

c) $t(4) = 0.5, p < 0.64$

Using vote-counting, it is tempting to say that a) has the largest effect since its p -value is 0.001. However, using formula:

$$d = \frac{2t}{\sqrt{df}}$$

Which estimates the effect-size (d , see section on effect sizes) from an independent sample t -test, where t is the t -test score and df the degrees of freedom of each experiment, we obtain that:

$$d = \frac{2(4.0)}{\sqrt{256}} = \frac{2(2.0)}{\sqrt{64}} = \frac{2(0.5)}{\sqrt{4}} = 0.5$$

Therefore, suggesting that despite differing p -values, the effect-size across studies a), b) and c), is similar.

An analogous situation occurs when the magnitude of a treatment effects is either large or small (i.e. $d = 0.8$ and $d = 0.2$, respectively. Based on Cohen, 1988 interpretative guidelines). Figure 1 shows the expected proportion of statistically significant results plotted as a function of sample size (Hedges and Olkin, 1985). In this figure, a “large”, “moderate” and “small” effect sizes are used to demonstrate that when a treatment effect is found to be small ($d = 0.20$) and sample sizes are less than 100, the expected proportion of significant results may not exceed 20%. Even when a moderate effect is found ($d = 0.50$), significant results only exceed 50% when sample sizes of approximately 70 are used. This suggests that if a review is comprised of a substantial number of studies with only small or moderate effects, it is likely that a large proportion of those studies may not have reached statistical significance which may lead a reviewer to either conclude that there is not

enough evidence to reject the null hypothesis or to suggest that there is no treatment effect at all (Hedges and Olkin, 1985).

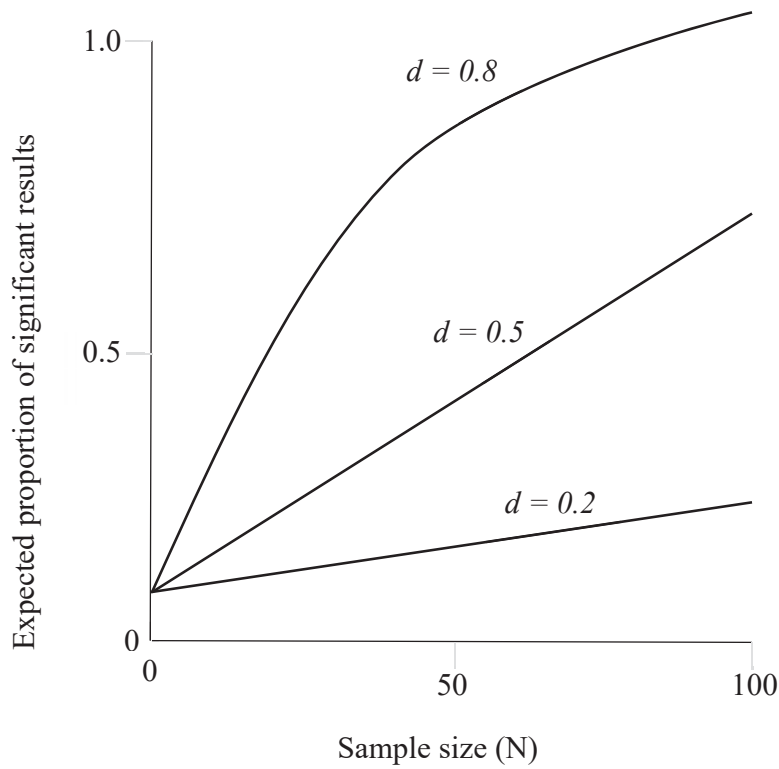


Figure 1. The expected proportion of significant results as a function of sample size and effect size (adapted from Hedges and Olkin, 1985)

Similarly, a systematic review is a type of literature review, however, it employs a detailed and explicit set of methods that allow for rigorous literature search and selection (Green et al 2006). A comprehensive literature search is based on a focused research question, which allows for the development of criteria to identify and appraise all empirical evidence around the chosen research question. The empirical evidence that meets the pre-specified eligibility criteria is used to answer the research question (Higgins and Green, 2011).

Unlike narrative reviews, qualitative systematic reviews use consistent and transparent methods to evaluate each study (Green et al 2006). This means that each piece of information that is extracted from a particular study will be treated similarly for all the included studies and therefore, it minimises the bias of subjectively including studies based on author's opinions or pre-conceptions about the research topic. Typically, a qualitative systematic review includes details of the search strategy and the methods used for assessing the eligibility of retrieved studies. Whilst, the methodology of a qualitative systematic review ensures its replicability (i.e. the methodology is available for the reader and can be repeated over time), it lacks the statistical combination of the extracted evidence. A systematic review that statistically combines the carefully extracted information is called a quantitative systematic review, also known as meta-analysis.

Meta-analytical methodology has been largely developed in the Health and Social Sciences (Sutton and Higgins, 2008). Meta-analysis provides a formal statistical framework to combine findings from independent studies, and thus could be viewed as an observational study of evidence (Egger et al. 1997). A meta-analytic review differs from a narrative one in that the available research evidence is actually quantified by using numerical effect-size estimates (Olkin, 1990). Nakagawa and Poulin (2012) summarized the methodological differences between narrative and meta-analytic reviews (Table 1) and explained that whilst meta-analysis will not fully replace narrative reviews for summarising theoretical, technical and methodological developments, it has been increasingly used as the preferred method to synthesize numerical results of primary empirical studies.

Table 1. Summary of methodological differences between narrative and meta-analytic reviews (taken from Nakagawa and Poulin, 2012)

Function	Narrative review		Meta-analysis	
	Can?	How?	Can?	How?
Hypothesis testing	Maybe	Logic, mental integration, sometimes with the aid of vote-counting	Yes	By estimating meta-analytic means and meta-regression coefficients
Heterogeneity identification	Maybe	Logic, sometime with the aid of vote-counting	Yes	By quantifying heterogeneity statistics (eg. Q and I^2)
Publication bias detection and correction	No	Not applicable	Yes	By visualisation of funnel plots and statistical methods (e.g. Egger's regression and trim-and-fill methods)
Hypothesis generation and future direction	Yes	By interpreting qualitative results and semi-quantitative methods	Yes	By interpreting quantitative results

The ability to quantitatively integrate a large number of studies has given scientists the opportunity to investigate and find trends that would otherwise not be possible with narrative reviews (Arthur Jr. et al. 2001) or other integrative methods. Figure 2 shows the number of meta-analytic publications in the past 26 years. This figure is based on entries according to the PubMed reference database, irrelevant of the research topic, and was obtained by using the keyword “meta-analysis” and its variants. Whilst not all retrieved records are meta-analysis, this figure confirms the large input that meta-analysis has in the development of new knowledge as there are more and more papers being published using this keyword. The next section of this literature review will outline some of the basic

concepts of meta-analysis while focusing on the methods used to plan, organise and implement meta-analysis for research synthesis.

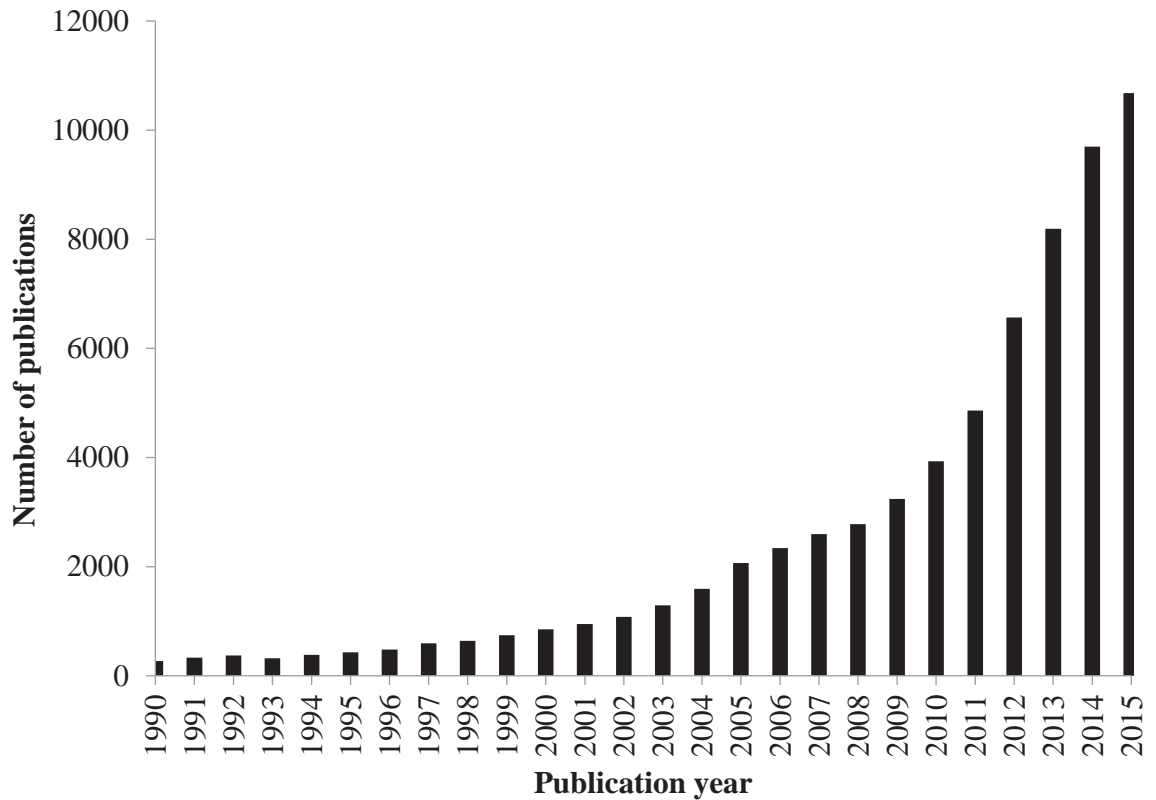


Figure 2. Number of meta-analysis publications in PubMed since 1990. Journal articles were search using the search string: meta-analysis OR metaanaly* OR meta-analy* OR meta analy* as publication type.

1.3 Meta-analysis – theory and practice

In 1982, Harris Cooper presented a five-stage model that conceptualized the process of reviewing published literature as a research process (Cooper, 1982; Hedges and Olkin, 1985), later modified into a six-stage process (Cooper, 2007). More important than the number of stages taken to complete a meta-analysis, is the cumulative content and the

attention to detail with which each stage is conducted. A brief explanation of each stage is as follows (Cooper et al. 2009; Arthur Jr et al. 2001; Egger et al. 1997):

1.3.1 Formulation of the research problem

The first and perhaps the most important aspect of planning a meta-analysis involves formulating and understanding the research questions (Pigott, 2012). This will aid identifying the key hypothesis and determining the variables that will aid the testing of the hypothesis prior to commencing the systematic search of the literature. For example, in determining the effect of maternal nutrition during pregnancy on lamb birth weight, the timing, length and severity of a nutritional manipulations can have an impact on the observed responses. This prior information is therefore helpful to determine what information needs to be obtained for quantitative analysis.

1.3.2 Collection of research evidence

The second major step in undertaking a meta-analysis is the systematic search of the literature. The literature search will determine whether a statistical meta-analysis can be undertaken or not based on the number of available studies. Cooper et al. (2009) and Higgins and Green (2011) have described the process of systematic literature searching in detail. Briefly, the search strategy requires the development of a plan that will allow the reliable identification of relevant information (Cooper et al. 2009). Understanding the research question allows the development of a list of relevant topic descriptors that will form the structure of the search term to be used in the different reference databases (Cooper et al. 2009). Classically, reference databases require a search term with a logical structure. Providing this structure to the search term is often done using Boolean operators linking

various concepts (Higgins and Green, 2011). For example, the Boolean “AND” is used to restrict or narrow a search (Cooper et al. 2009) by linking a number of concepts that are of particular interest and relevance to the study (e.g. type of treatment AND timing of treatment AND length of treatment, etc.). The Boolean “OR” is used to expand or broaden the search (Cooper et al. 2009) by joining concepts together so that the citations retrieved include either of the terms comprised in the search term (i.e. pregnancy OR gestation OR prenatal). The Boolean “NOT” is used to exclude terms that are not relevant to the review. For example, *NOT mice* would exclude from the search studies mentioning mice. Finally, the search term needs to be adapted to match the specific search string formatting requirements of each database.

Cooper et al. (2009) explained that the replicability and accuracy of a systematic review and meta-analysis depends highly on the thoroughness of the literature search. Rothstein et al. (2005) pointed out that if a sample of studies used in a systematic review or meta-analysis is biased, the validity of the results would be seriously threatened no matter how systematic the process of retrieving those studies was. Even when comprehensive electronic searches are performed, they rarely retrieve all the available literature (Egger and Smith, 2001). It is therefore necessary to inspect or examine the reference lists of relevant or highly cited references from the main searches (i.e. reviews, key papers) for possible studies that were not found in the initial search and to use other sources and strategies to avoid collecting a biased sample of studies.

The most common biases related to literature search are: (i) classical publication bias, also known as the “file drawer” problem, which refers to the bias in published literature towards

statistically significant results (Gøtzche, 1987, Pigott, 2012), (ii) language bias, or the process of selectively searching for English-only material (Egger et al. 1997), (iii) availability bias, or selection of only material that is easily accessible, (iv) duplication bias, resulting from statistically significant results being published more than once (Tramer et al. 1997), and (v) incomplete reporting bias, resulting from some authors selectively withholding statistically non-significant results when reporting outcomes (Chan et al. 2004).

1.3.3 Evaluation and identification of relevant studies

After collecting the available evidence, it is necessary to specify the criteria used to include or exclude primary studies. Since the decision rules applied to assess the eligibility of studies in a meta-analysis is likely to affect its outcome, it is critical to explicitly state the underlying inclusion/exclusion criteria. Information related to the decisions taken during this step needs to be recorded as this is later used to report the number of excluded studies and the reasons for exclusion. The process of evaluating studies also includes the development of a coding protocol that outlines the information that needs to be extracted from each included study (Pigott, 2012) in order to create a dataset suitable for meta-analysis.

1.3.4 Analyses and integration of evidence from individual studies

1.3.4.1 Selecting an effect size statistic

After careful consideration and identification of studies to be included, a dataset is created that contains the summary data of each individual study. For meta-analysis, it is essential to have a statistic that reflects the magnitude of a relationship between two variables (Cooper

et al. 2009) and can be compared across studies. In meta-analysis, there are three categories of effect size statistics that are traditionally used (Borenstein et al. 2009). The first category includes effect size statistics that are based on the computation of a standardized statistic between two means (Nakagawa & Santos 2012). This category includes the standardized mean difference Cohen's d (Cohen, 1988) or Hedges' g (Hedges, 1981) and the response ratio (Hedges et al. 1999; Lajeunesse, 2011). The second category corresponds to a metric representing a relationship between two variables, the correlation coefficient, r (Nakagawa and Santos, 2012; Cooper et al. 2009). The third category encompasses measurements made on binary scales (Cooper et al. 2009), some of which are the odds ratio, relative risk and risk difference (Nakagawa and Santos, 2012).

Nakagawa and Santos (2012) explained that these effect size statistics have two characteristics in common that are required for meta-analysis: i) they or their transformations are normally distributed and ii) they or their transformations' sampling variances are estimable from formulas. This section of the literature review will focus on the most common effect size statistic used throughout this thesis: the standardized mean difference (eg. Cohen's d and Hedges' g). Detailed mathematical definitions of these and other effect size statistics have been discussed in detail by Grissom and Kim, (2005), Nakagawa and Cuthill, (2007), Hillbrand, (2008), Cooper et al. (2009), Borenstein et al. (2009), Schielzeth, (2010), Higgins & Green, (2011) and Lajeunesse, (2011, 2015).

1.3.4.1.1 Calculation of the standardized mean difference

The first step in a meta-analysis is calculating a summary statistic for each study that was included in the systematic review. Glass (1976) advocated for the need to create an index

that would be comparable across studies and proposed the standardized mean difference as a measure of effect size. Glass's estimator of effect size is given by:

$$d_i = \frac{\bar{X}_i^{exp} - \bar{X}_i^{con}}{S_i^{con}}$$

Where \bar{X}_i^{exp} and \bar{X}_i^{con} are the experimental and control groups means for the i^{th} experiment and S_i^{con} is the sample standard deviation of the control groups of the i^{th} experiment.

Glass (1976) argued that when several treatments were compared to a control group, pooling two variances could lead to different values if an identical mean difference is found within the same experiment. Hedges (1981) argued that this approach depended on the assumption that the standard deviation of each group will surely differ; an argument that does not apply when a model of equal population variance is assumed (i.e. as in most parametric data analysis techniques, Cooper et al. 2009). As a consequence, if S_i^{exp} and S_i^{con} are the standard deviations of the experimental and control groups, n_1 and n_2 are the two groups' sample sizes and it is assumed that the underlying population standard deviations are the same ($\sigma_1 = \sigma_2 = \sigma$; Cooper et al. 2009), a modified estimator of the standardized mean difference can be obtained using the pooled estimate of the standard deviation, therefore (Hedges, 1981):

$$d_i = \frac{\bar{X}_i^{exp} - \bar{X}_i^{con}}{S_i}$$

Where S_i is the within-groups standard deviation, pooled across groups, given by:

$$S_{pooled} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

This approach was originally suggested by Jacob Cohen as a population parameter when describing the magnitude of an effect in terms of the degrees of departure from no effect

that he used in statistical power analysis (Cohen, 1988). For this reason, the index d is often referred to as Cohen's d .

Cooper et al. (2009) explained that a very good approximation of the variance of d is given by:

$$v_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)}$$

where $\frac{n_1 + n_2}{n_1 n_2}$ denoted the uncertainty of the estimate of the mean difference and $\frac{d^2}{2(n_1 + n_2)}$ expresses the uncertainty in estimating S_{pooled} . The standard error of d is the square root of v_d :

$$SE_d = \sqrt{v_d}$$

Now, let δ be the population standardized mean difference parameter. Hedges (1981) found that d has a slight bias that tends to overestimate the value of δ . He proved that as the degrees of freedom (df) available to estimate S_{pooled} increase, the estimate d_i is approximately the true value of δ . He explained that as the df tend to infinity, the mean of d_i tends to δ , whilst the variance of d (v_d) tends to zero; however, this is not the case for small sample sizes. Hedges (1981) demonstrated that in a collection of studies with sample sizes of 5 subjects per group, the estimator d resulted in an overestimation of δ of approximately 25%. He suggested that an adjustment factor is needed to correct for this bias, which is given by:

$$J(df) = 1 - \frac{3}{4df - 1}$$

Where df are the degrees of freedom used to estimate S_{pooled} , which for two independent groups is calculated by $n_1 + n_2 - 2$. Consequently, the unbiased estimator g proposed by Hedges (1981) is also referred to as Hedges' g and is given by (Cooper et al. 2009):

$$g = J(df)d$$

Its variance (v_g) and standard error (SE_g) are then given by:

$$v_g = [J(df)]^2 v_d$$

$$SE_g = \sqrt{v_g}$$

1.3.4.2 Estimating the overall effect across studies; the meta-analytic mean

The next step in undertaking a meta-analysis is to calculate the overall treatment effect or meta-analytic mean. There are two traditional meta-analytic models: i) fixed-effect, and ii) random-effects models. Each model uses different assumptions about the nature of the studies and the way in which weights are assigned to those studies because of those assumptions. Hedges and Olkin (1985), Borenstein et al. (2009), Lipsey and Wilson (2001), Cooper et al. (2009) and Nakagawa and Santos (2012) provide clear mathematical explanations of fixed and random effects models. This section, focuses on the pros and cons of using traditional meta-analytic models in biological datasets and some of the statistical developments that have helped overcome specific issues of biological meta-analysis.

1.3.4.2.1 Fixed-effect model

The term “effect” (i.e. singular effect) is used to denote the assumption that under the fixed-effect model there is only one true affect, or meta-analytic mean, that is common / shared across all included studies (Borenstein et al. 2009; Nakagawa and Santos, 2012). Under the

fixed-effect model, the observed effects are assumed to be sampled from a distribution with the mean at true effect θ , and variance σ^2 . A schematic representation of a fixed-effect model is shown in Figure 3. Both studies are assumed to be drawn from a population of true mean 100, however, their observed mean lies at some distance from the true mean. It is assumed that differences between studies are irrelevant (since they measure the same effect) and that any difference among studies is only due to the error in estimating that particular effect size (Cooper et al. 2009; see Figure 3).

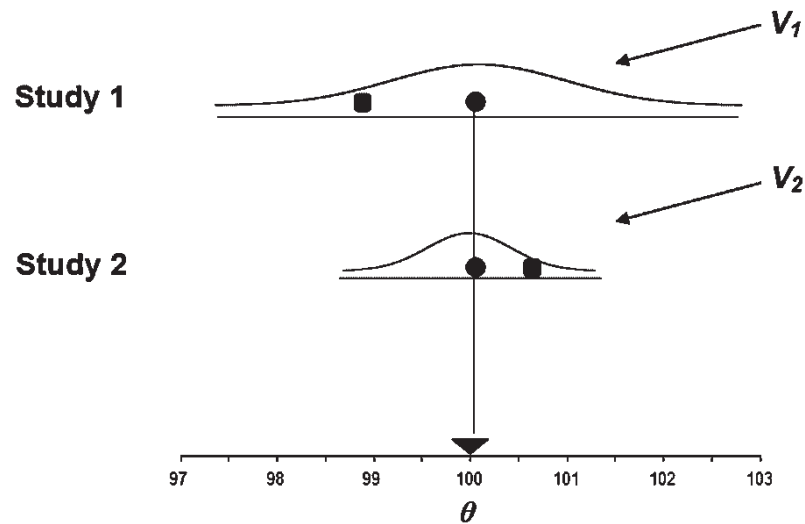


Figure 3. Schematic representation of the fixed-effect model (reprinted from Borenstein et al. 2010). • represents the common mean ($\theta = 100$) across studies, i.e. the true effect magnitude. ■ represents the observed mean for each particular study, and V_1 and V_2 represent the variance of the mean in study 1 and 2 in relation to θ .

Borenstein et al. (2009b) suggested that using a fixed-effect model in meta-analysis required two specific conditions. First, to assume that all included studies are functionally identical; and second, the goal of the analysis needs to be to compute an overall effect for

the identified population and not to generalize to other populations. The disadvantage of the fixed-effect model is that the conditions to fit the model are rarely met, especially in biological meta-analysis where studies differ in study design, the mixes of participants, species and other random factors (Nakagawa and Santos, 2012). This suggests that there may be different true effects sizes underlying different studies.

1.3.4.2.2 Random-effects model

The word “effects” (i.e. plural, many effects) is used to denote an array of effects sizes that can differ from study to study. The goal in a random-effects model is not to estimate one overall true effect across studies but rather to estimate the mean of a distribution of effects (Borenstein et al. 2009b). In other words, the observed effects (θ_i ; assuming one effect size per study) are sampled from a population of effects with true effect θ and variance σ^2 . Under the random-effects model, each study is assumed to have been sampled from a distribution of studies, thus suggesting that the true effect θ is in itself sampled from a distribution of effects with mean μ and variance τ^2 (commonly called the variance component; Figure 4). Consequently, each effect size has two components of variance, one due to sampling error and a second one from the underlying distribution (also known as the between-study variance).

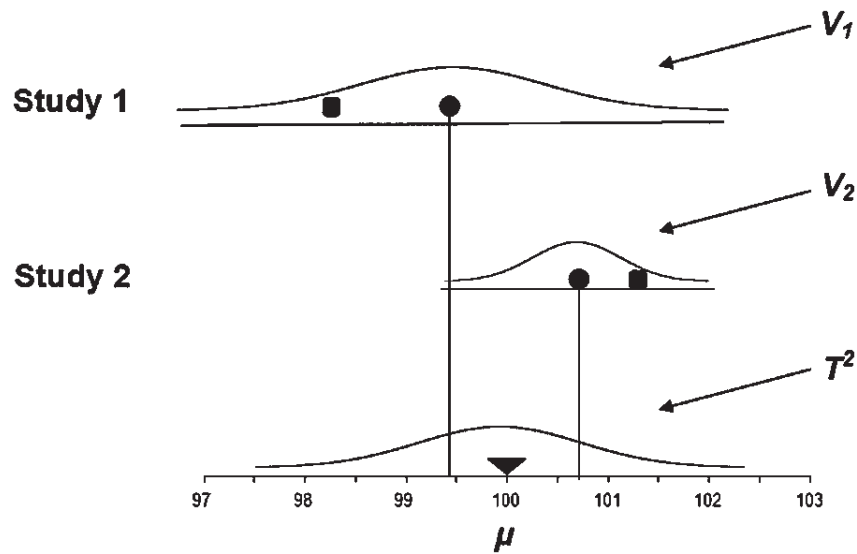


Figure 4. Schematic representation of the random-effects model (reprinted from Borenstein et al. 2010). For each study, the sample mean is represented by a full circle (•). In this case the true effect is not fixed and so it varies from Study 1 to Study 2 since they were samples from the distribution at the bottom where μ represents the mean of the distribution of true effects with variance τ^2 . The observed mean (■) in Study 1 and 2 differ from the true mean (•) of each particular population because they use a finite number of individuals to estimate the effect.

Nakagawa and Santos (2012) argued that despite the practicality of random-effects models, these models are designed for meta-analyses where each included study contributes only one effect size to the analysis (i.e. $N_{study} = N_{effect-size}$). Because the studies are statistically independent, their effect sizes are assumed to be also independent. However, the situation is not always so simple and studies may provide more than one effect-size to the meta-analysis ($N_{effect-size} > N_{study}$), thereby, violating the assumption that observations within a dataset are independent from each other. In this case, the degree of effect-size dependence needs to be accounted for in the meta-analysis (Gleser and Olkin, 2009).

1.3.4.2.3 *Dealing with effect-size dependence*

The problem with dependent effect-sizes, as pointed out by Van den Noorgate et al. (2012), is that they are less informative than independent effect-sizes. When two effect-sizes are correlated (for example, $R^2 = 1$) and used as independent effect-sizes for meta-analysis, we are using the same information twice because each outcome or effect-size provides the same amount of information to the analysis. If this is the case, standard errors of the meta-analytic means will be underestimated resulting in overestimation of confidence intervals (Becker, 2000; Van den Noorgate et al. 2012).

There are many sources of dependence (see Noble et al. 2017), but they can be categorised as either known or unknown (Cheung, 2014). The dependence is said to be known when is introduced by the meta-analyst (Stevens and Taylor, 2009, Cheung, 2014). A typical example of this type of effect-size dependence and one that is dealt with throughout this thesis is the case of *multiple-treatment studies* (Gleser and Olkin, 1994, 2009), where a number of variants of a treatment are compared to a common / shared control group. For example, when studying the effect of maternal nutrition during pregnancy on fetal weight, Brennan et al. (2005) used one control group of ewes fed to meet their pregnancy maintenance requirements to compare with four experimental groups that were underfed at four periods of pregnancy (i.e. treatment 1: 0-30 days, treatment 2: 31-65 days, treatment 3: 66-110 days and treatments 4: 0-110 days post-conception). In this case, the source of dependence is not intrinsic to the design of the study but rather in the way the effect sizes are calculated for meta-analysis. In meta-analysis, because the variance of the control group is used to standardise the mean difference for each variant of the treatment (see *Calculation of the standardized mean differences* above), their effect sizes will be correlated and

consequently this needs to be taken into account for in the meta-analysis to avoid overestimation of treatment estimates. To deal with this type of effect-size dependence, the sampling variance-covariance matrix needs to be calculated, as in Gleser and Olkin (1994, 2009), prior to fitting the model. Becker (2000), Gleser and Olkin (1994, 2009), Stevens and Taylor (2009), Lajeunesse (2011) and Noble et al. (2017) provide mathematical descriptions, methods and additional references to deal with many of the cases of “known” dependence.

Unlike known dependence, unknown dependence is introduced at the study level and arises due to the hierarchical structure of some datasets (Nakagawa and Santos, 2012). For example, effect-sizes estimated from the same research group are likely to be more similar than those estimated by a different research group. This is because effect-sizes are influenced by the way studies were conducted, the characteristics of the populations being studied, the way these populations were sampled and the people involved in recording the data (Cooper, 2009). To deal with these problems of dependence in meta-analysis, the use of multilevel models, which are an extension of the random-effects models, had been advocated (Nakagawa and Santos, 2012).

1.3.4.2.4 Multilevel meta-analytic models

In meta-analysis context, multilevel models are useful to deal with both known and unknown dependence since they relax the effect-size independence assumption of fixed effect and random effects model (Nakagawa et al. 2017). A simple multilevel model is depicted in Figure 5, where multiple effect sizes are obtained from various studies and used for meta-analysis. Similar to a random effects model, each study is assumed to be sampled

from a distribution of studies (see Figure 5a), thereby having their own study-specific effect (green squares and green solid lines) that deviates from the overall mean (b_0) by s_i (green dotted lines), which is distributed with variance τ^2 , also known as the between-study variance (green curves). However, since each study provides the meta-analysis with more than one effect-size (see Figure 5b), the within-study variance can be estimated and separated from the sampling variance (Hadfield and Nakagawa, 2010). Therefore, in Figure 5b, u_{ij} is the within-study deviation from s_i of the j th effect-size for the i th study and is distributed with a variance σ^2 known as the within-study variance (Figure 5b – blue curves), with e_{ij} being the sampling deviation from u_{ij} . Various programs like *ASReml* (Gilmour et al. 2002), *BUGS* (Lunn et al. 2000) and the R package *MCMCglmm* (Hadfield 2010) can be used to implement these simple multilevel meta-analytic models. Nakagawa and Santos (2012), Van den Noortgate et al. (2012) and Cheung (2014) provide further mathematical explanations about multilevel modelling and give multiple examples on how to extend these meta-analytic models to included more levels in the data.

Multilevel meta-analytic model

$$y_{ij} = b_0 + s_i + u_{ij} + e_{ij}$$

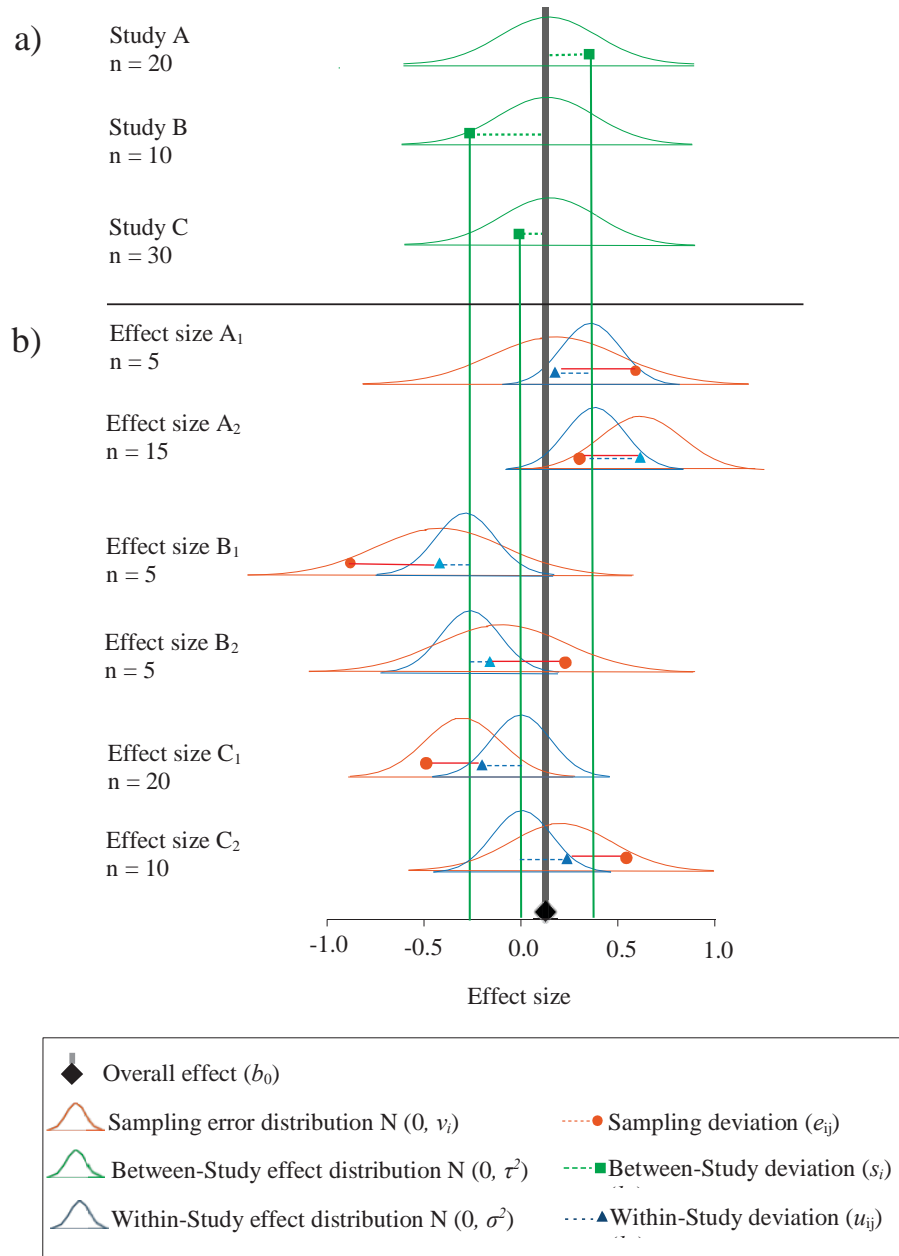


Figure 5. Schematic representation of a multilevel meta-analytic model (adapted from Nakagawa et al. 2017).

1.3.5 Interpretation of the cumulative evidence

The next step in conducting a meta-analysis is to summarize the cumulative evidence based on the strength, generalizability and limitations of the meta-analysis. This step often involves the assessment of heterogeneity and the potential sources of this variability in study results, the estimation of publication bias and the use of sensitivity analyses to test arbitrary or unclear decision made throughout the meta-analysis process or chance effects related to influential studies.

1.3.5.1 Quantifying and explaining heterogeneity

So far, meta-analysis has been used to estimate the average effect across a number of studies answering a similar question. When the magnitude of the effects of each included study is similar, deriving conclusions from our estimate becomes relatively simple. On the other hand, when results are somehow different, conclusions are less clear (Higgins and Thompson, 2003). One of the primary goals of meta-analysis is to understand to what extent the results from primary studies are consistent (or inconsistent) with each other. In this way, we are able to assess the “combinability” of the included studies.

The assessment of heterogeneity is one of the most important parts of a meta-analysis (Higgins et al. 2003; Nakagawa and Santos, 2012). This is because the presence of true heterogeneity affects the decision of what statistical model needs to be used (Huedo-Medina et al. (2006), therefore, it directly affects the reliability of the estimated meta-analytic mean (Nakagawa and Santos, 2012). In general terms, the test of heterogeneity estimates whether there are true differences underlying the results from the included studies irrelevant of the sampling error. Traditionally, heterogeneity has been assessed using either

the Q -test proposed by Cochran (1954), which provides information on whether there is statistically significant heterogeneity or the I^2 index defined by Higgins and Thompson (2002), which provides information on the extent of heterogeneity (which can be categorised as small, medium or large heterogeneity; Higgins et al. 2003).

The Q statistic is calculated as the sum of weighted squared deviations of each study's estimate from the overall effect estimate. Statistical significance of Q is tested against a chi-square distribution with $k-1$ degrees of freedom, k being the number of studies (for detailed description of this test see Cochran, 1954 and Higgins et al. 2003). Hardy and Thompson (1998) demonstrated that this test has low power to detect heterogeneity when the number of included studies is too small (i.e. $n = 10$) and it has been suggested that a value of 0.10 is used as a cut-off for significance (Higgins et al. 2003). Higgins et al. (2003) also demonstrated that the Q -test has too much power when there is a large number of studies. They showed that by using the Q -test to determine heterogeneity in a meta-analysis of 135 trials with over 15 000 participants, a p -value of 0.005 was obtained, suggesting significant heterogeneity in the data. They argued that this p -value does not describe the extent to which heterogeneity affects the results of the meta-analysis. Using the I^2 index on the same dataset, they showed that whilst heterogeneity was present ($I^2 = 26\%$), it was unlikely to have a major input on the estimated effects.

The I^2 index is an improvement over the Q -test as a measure of heterogeneity in meta-analysis (Nakagawa and Santos, 2012). Rather than focusing on statistical significance, the I^2 index is unit-less (as many other effect-sizes used in meta-analysis) and focuses on

quantifying the degree of between-study variance that is not due to chance alone (Higgins et al. 2003). Using the notation of Nakagawa and Santos (2012), the I^2 index is defined by:

$$I^2 = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_m^2}$$

where σ_u^2 is the between-study variance and σ_m^2 is the typical sampling error variance (see Higgins and Thompson, 2002 and Nakagawa and Santos, 2012 for how to estimate σ_m^2 , see also below). I^2 values of 25%, 50% and 75% are considered low, moderate or high heterogeneity for meta-analysis purposes (Higgins et al. 2003). Nakagawa and Santos (2012; cf. Cheung, 2014) extended the definition of I^2 proposed by Higgins and Thompson (2002) to suit multilevel meta-analytic model. In this extended I^2 version, the sum of all variance components is used instead of just the between-study variance, then:

$$I^2 = \frac{\sigma_t^2 - \sigma_m^2}{\sigma_t^2}$$

where σ_t^2 is the sum of all variance components and σ_m^2 is the typical sampling error variance calculated as:

$$\sigma_m^2 = \frac{\sum_{i=1}^k w_i(k-1)}{(\sum_{i=1}^k w)^2 - \sum_{i=1}^k w_i^2}$$

where w_i is the inverse of the i th measurement error variance associated with the i th effect-size estimate ($i = 1, \dots, k$).

After heterogeneity has been detected (and quantified), the next step is to find possible explanatory variables that can account for some of that variation in study results. In meta-analysis, these explanatory variables are called moderators (i.e. covariates or categorical predictors) and have been defined *a priori* during the first two stages of the meta-analytic

process. In meta-analysis, moderators are used to build a mixed-effects model (that is, a model that assumes that heterogeneity stems from both fixed and random effects), which is usually referred to as meta-regression. Unaccounted variance in the meta-analysis can be therefore explored with meta-regression models (Harrison, 2011). Although, more complex models require a larger sample of studies (Pigott, 2012), and whilst meta-regression is advised to explore the conditional relationship among the selected moderators and effect-size magnitude, it comes at a cost of loss of power (Lipsey and Wilson, 2001, Nakagawa and Santos, 2012). Nakagawa and Santos (2012) recommended meta-regression models as the primary meta-analytic models presented in biological meta-analyses, because heterogeneity is almost always present in biological datasets. Although, they also suggested that any meta-analytic model used for analysis should compromise between complexity and the nature of the data, and urged to run several alternative models to confirm the robustness of the estimated results.

1.3.5.2 Publication bias

Rothstein et al. (2005) defined the term publication bias as the case when the published research is not representative of the research undertaken in a certain area. This often occurs when experiments are published (or not published) depending on the direction and statistical significance of the results (Sutton et al. 2002, Sterne et al. 2001). Because of this, publication bias has the potential to promote false conclusions in the review process (Dickersin, 2005), therefore, is also considered as a threat to the validity of meta-analysis (Rothstein et al. 2005, Rothstein, 2008). Since publication bias may seriously affect the conclusions of a meta-analysis, various methods have been devised to detect and correct for the effects of publication bias (Table 2. For a dedicated book about publication bias see

Rothstein et al. 2005). This section focuses on the methods that have been used throughout this thesis to detect and correct for publication bias.

Table 2. Commonly used methods to detect and correct for publication bias and some of the caveats in the listed methods. References are provided for the papers that propped the methodology and also for those reporting on some of the caveats in the methods.

Method	What does it measure?	Limitations
Funnel plots (Light and Pillemer, 1984)	Data distribution asymmetry	Provides only a visual assessment and is open to interpretation (Lau et al. 2006). Possible other reasons for funnel plot asymmetry rather than just publication bias (Egger et al. 1997).
Rank correlation test (Begg and Mazumdar, 1994)	Association between effect estimates and their sampling variances	Relies on sample size. Low power in small meta-analyses (Sterne et al. 2001). Should not be used when effect-sizes are not independent (Nakagawa and Santos, 2012).
Egger's regression method (Egger et al. 1997)	Statistical test of funnel plot asymmetry	Better than rank correlation but still relies on sample size (Sterne and Egger, 2005). Significant asymmetry can also reflect heterogeneity. Should not be used when effect-sizes are not independent (Nakagawa and Santos, 2012).
Failsafe N or File-Drawer Number (Rosenthal, 1979)	Estimates the number of new studies with null result required to make the overall estimate not significant	Assumes all published and unpublished studies are of same size. Choice of zero as average effect of unpublished studies is arbitrary. Fewer studies would be required if average effect is less than zero (Beggs and Berlin, 1988). Heterogeneity is ignored (Iyengar and Greenhouse, 1988). No estimation of true effect. Method based only on p -values (Sutton, 2009).
Trim-and-fill method (Duval and Tweedie, 2000a, 2000b)	Identify and correct funnel plot asymmetry. Adjusts meta-analytic mean in the presence of publication bias.	If large heterogeneity is present, the test underestimates the adjusted estimate (Peters et al. 2007). Poor performance when there is no publication bias (Terrin et al. 2003). Designed only for independent effect-sizes (Nakagawa and Santos, 2012).

One of the most widely used methods to detect publication bias is the visual assessment of funnel plots for the presence of data distribution asymmetry. Funnel plots are, simply, scatter plots of effect sizes (usually on the horizontal axis) against some measure of study size or its precision (i.e. standard error, inverse variance; Sterne et al. 2011; for a list on vertical axis selection and their corresponding properties, see Sterne et al. 2005, page 86). In the absence of publication bias, data points (that is, the effect sizes calculated from the data) are symmetrically distributed around the meta-analytic mean, usually in a funnel shape (Figure 6a). The funnel shape results from the precision in estimating an underlying treatment effect, with smaller studies having a wider dispersion of results (at the bottom of the graph) and a narrower array of results derived from larger studies (at the top of the graph). On the contrary, Figure 6b depicts an asymmetrical funnel plot (indicative of publication bias), with some small studies showing non-significant results “missing” on the right-hand side of the funnel plot. In this case, the estimated meta-analytic mean is overestimated because studies showing no positive effect (the right-hand side) are missing and not taken into account in the analysis.

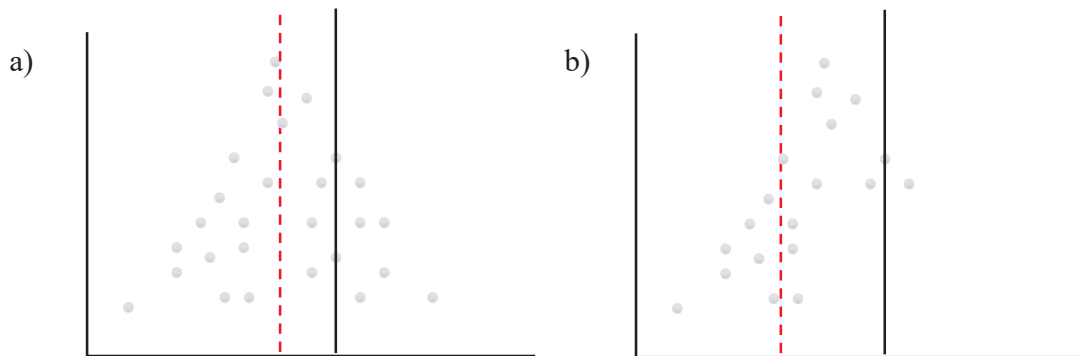


Figure 6. Examples of hypothetical a) symmetrical and b) asymmetrical funnel plots, where the horizontal axis represents the treatment effects estimated from individual studies and the vertical axis represents some measure of study size (e.g. standard error on a reverse scale that places larger studies on top of the graph). Solid line represents zero effect. Dashed line represents the meta-analytic mean (Based on Sterne et al. 2005). More details in the text.

Despite the widespread use of funnel plots as visual aids to assess publication bias, their evaluation is subjective (Sterne et al. 2005) and open to interpretation (Lau et al. 2006), because it is not a formal statistical test. In addition, data distribution asymmetry does not only result from publication bias (Egger et al. 1997). Other types of selection bias (i.e. language bias or selective outcome reporting), heterogeneity, data irregularities, poor choice of effect-size measure or, simply, chance may also result in funnel plot asymmetry (see Egger et al. 1997 for a list of additional sources of funnel plot asymmetry).

To formally test for funnel plot asymmetry, Egger et al. (1997) proposed that a simple linear regression where the standard normal deviate z_i (i.e. $z_i = y_i/\sqrt{w_i}$, where y_i is the effect size of study i and w is the inverse of the sampling variance) is regressed against $\sqrt{w_i}$

(Egger et al. 1997, Sutton, 2009). The intercept of this regression provides a measure of asymmetry (Sutton, 2009) and when significant, it can be concluded that there is evidence of publication bias (Egger et al. 1997). This test appears to be more reliable in detecting publication bias than the rank correlation test proposed by Begg and Mazumdar (1994, see also Egger et al. 1997, Sterne, 2000), however, there are three major limitations to this test. First, the test has low power when binary outcomes are considered (i.e. odd ratio; see Macaskill et al. 2001, Deeks et al. 2005 for further mathematical explanations). Second, Egger's regression test relies on the number of studies included for meta-analysis, and consequently, has low power in small meta-analyses (i.e. fewer than 10 studies; Sterne et al. 2000). Lastly, Egger's regression test is designed for meta-analysis of independent effect-sizes, suggesting that it cannot be directly used for multilevel meta-analytic models (Nakagawa and Santos, 2012). Nakagawa and Santos (2012) proposed that the Egger's regression approach should use meta-regression residuals rather than actual effect sizes. This is because residuals are independent from each other and because inclusion of moderators takes into account for some of the heterogeneity across the dataset (Nakagawa and Santos, 2012). In this extension of the Egger's regression approach, a significant intercept is interpreted as evidence of publication bias after controlling for some of the heterogeneity in the data (Nakagawa and Santos, 2012).

If publication bias is detected, it is necessary to assess the impact of the potentially missing studies on the overall estimate from the meta-analysis. The trim-and-fill method (Duval and Tweedie, 2000a, 2000b) is the most popular technique used to adjust meta-analyses for the effects of publication bias (Borenstein, 2005). This non-parametric test relies on estimating the number of missing studies (using an iterative algorithm), so that funnel plot asymmetry

is corrected (see Duval, 2005, for a clear definition of the “trimming” and “filling” process, see also Table 1 for limitations of the method). Briefly, when the number of missing studies is determined, they are “trimmed” off the asymmetric part of the funnel, leaving a more symmetrical funnel plot. With this new trimmed dataset, a new overall estimate is calculated at the new centre of the funnel. The trimmed studies are reinstated in the plot, along with the imputed studies (mirror images of those trimmed) on the other side of the plot (see Figure 7). Finally, the observed and imputed studies are used to estimate the standard error of the overall effect (Figure 7). In the case of multilevel meta-analyses, Nakagawa and Santos (2012) proposed a similar approach to their modification of the Egger’s regression approach where the trim-and-fill method is applied to meta-regression residuals. Irrelevant of the method used, the new estimate calculated after applying the trim-and-fill method should be used as a form of sensitivity analysis (Duval, 2005).

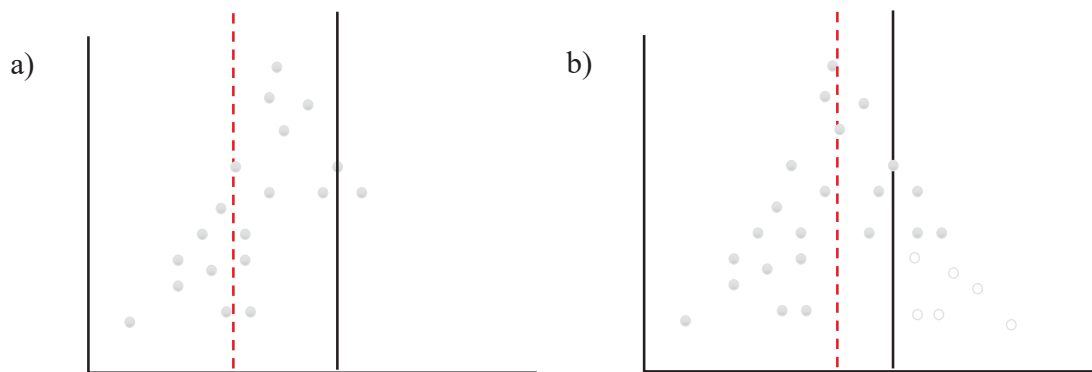


Figure 7. Hypothetical examples of the results of a trim-and-fill method: a) an asymmetrical funnel plot suggesting possible publication bias due to missing studies in the bottom-right of the plot, b) the “filled” and more symmetrical funnel plot including the imputed studies as mirror images of those on the left hand side (open circles). Solid line represents zero effect. Dashed line represents the meta-analytic mean a) before and b) after adjusting for publication bias.

1.3.5.3 Sensitivity analysis

A sensitivity analysis is simply a repeat of the primary analysis but uses alternative decision to those primarily used to obtain the overall estimate (Higgins and Green, 2011). At every step in the process of conducting a meta-analysis, a sequence of decisions was made in order to get the answer to the meta-analytical question (estimating overall effect or effects of moderators). Whilst many of these decisions are easily justified, as it is the case of excluding a particular study based on the predetermined selection criteria, some other decision could be somewhat arbitrary and potentially unjustified to the reader (Greenhouse and Iyengar, 2009). For instance, including or omitting a particular study with an unusual or exaggerated effect-size has the potential to affect the overall estimate. Another example is the choice of including only peer-reviewed published studies and not papers from conference proceedings or dissertations (Greenhouse and Iyengar, 2009). In either case, it is desirable to prove that the results from the meta-analysis are not dependent on such arbitrary decision (Higgins and Green, 2011), usually by conducting a sensitivity analysis. This sensitivity analysis is unique to each meta-analysis and many resources are available to help resolving particular issues (e.g. in the case of missing information affecting the meta-analysis, the use of missing data imputation could help elucidate potential problems). If the overall conclusion, however, is not affected by these arbitrary decisions, after a sensitivity analysis is carried out, the results from the meta-analysis can be regarded as having a greater degree of certainty. For a dedicated summary on sensitivity analysis and diagnostics see Greenhouse and Iyengar (2009).

1.3.6 Presentation of meta-analysis methods and results

The last step in conducting a meta-analysis involves reporting the overall findings and the interpretation of these results. Meta-analysis of effect-size statistics is slowly gaining a place in the Animal Sciences (see Lean et al. 2006 and Duffield et al. 2012 for an example of meta-analysis in animal nutrition), and it's undoubtedly one of the fastest growing statistical tools currently available to summarise results from published literature (Engstrom, 2014). A reporting protocol that is specific to Animal Science has not yet been developed, however, many research protocols are available that describe a minimum set of information that is required to be reported in a meta-analysis (see Moher et al. 2009 and de Vries et al. 2015 for reporting protocols used in medicine for meta-analyses of human and laboratory animal experiments, respectively; see also Clarke, 2009 for a checklist of meta-analysis reporting standards). Animal scientists can adapt these protocols to improve the reporting quality of meta-analyses of animal trials.

Following the recommendation by Nakagawa and Santos (2012) given for meta-analyses in biological sciences, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement proposed by Moher et al. (2009) has been adopted throughout this thesis (where applicable). The PRISMA statement consists of a 27-item checklist essential for transparent reporting of a systematic review (see Moher et al. 2009 for the checklist and Liberati et al. 2009 for detailed explanations and examples of every item in the checklist). In addition, it offers a four-phase flow diagram that identifies the main phases of a systematic review (Figure 8). This diagram offers readers the opportunity to view and assess the meta-analytic process from data collection to the final decisions for the inclusion and exclusion of studies.

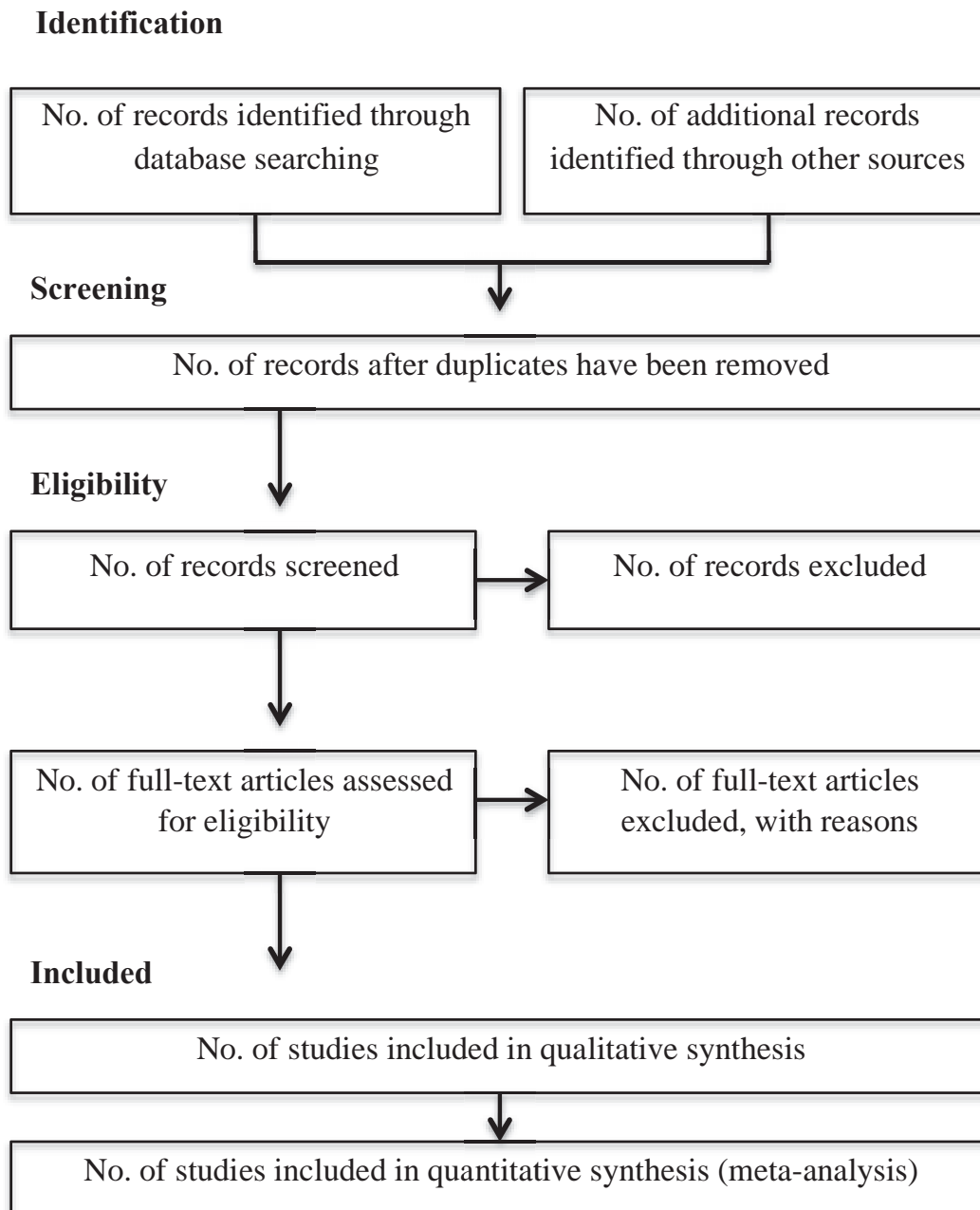


Figure 8. Four-phase diagram depicting the flow of information through the different phases of a systematic review (adapted from Moher et al. 2009).

1.4 Summary and research objectives

Meta-analysis provides us with the statistical tools to do two things (Harrison, 2011): first, meta-analysis allows the estimation of a mean treatment effect across a number of replicated experiments, and; second, meta-analysis allows determining the amount of change in a given dependent variable that is due to experimental factors and provides us with the tools to explain varying results using potential predictor variables called moderators. In the remainder of this thesis, the meta-analytic tools reviewed in the present chapter were used to quantify the degree to which late-gestation fetal weight (Chapter 2), lamb birth weight (Chapter 3) and weaning weight (Chapter 4) are affected by changes in the ewe nutrition during pregnancy. The objectives of the next three chapters were threefold: Firstly, to estimate overall treatment effects across nutritional manipulations. Secondly, to quantify the amount of variation in study results (i.e. heterogeneity) and identify different experimental factors that account for the disparity in responses to the varying nutritional regimens across studies. Thirdly, the combined results and limitations identified in these meta-analyses were used to find areas where more research is needed. Based on these gaps in the knowledge, a field trial (Chapter 5) was designed to help clarify one of those areas that remain poorly understood. Finally, the results across all the different analyses were discussed in terms of farm productivity, the feeding management of the sheep flock and the future research that is needed to develop the knowledge of the effect of maternal nutrition during pregnancy on fetal and lamb growth (Chapter 6).

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Chapter 2: Changes in late gestation fetal weight via maternal nutrition: meta-analytic insights from studies using adult sheep.

2.1 Abstract

Assessment of maternal nutritional programming studies can be challenging because consistent biological effects are difficult to observe in studies with relatively small sample sizes and that vary in a wide variety of experimental, maternal and offspring related factor. Therefore, the present study uses a meta-analytic approach to determine the variation in late gestation fetal weight (LGFW) responses across 55 studies and to quantify the contribution of these factors to the variation in observed results. Traditional meta-analytic and meta-regression models were used to estimate overall effects and the input of various predictor variables in explaining the heterogeneity in the data, respectively. Results suggests that early- and mid-pregnancy undernutrition have no significant effect on LGFW, whereas undernutrition during late-pregnancy was associated with lighter fetuses (-0.79, 95% Highest posterior density (HPD) interval = -1.09 to -0.47). This negative effect of undernutrition was intensified as the length of the undernutrition periods increased (-0.16, 95% HPD = -0.31 to -0.03). Additionally, maternal overnutrition had no overall effect on LGFW. However, responses across studies were, to some extent, controlled by litter size and the length of overnutrition. This meta-analysis demonstrated that correct management of ewe nutrition during late pregnancy is essential to achieving optimum fetal weight prior to lambing.

Key words: meta-analysis, fetal weight, sheep, maternal nutrition

2.2 Introduction

In production animals, variations in fetal growth are largely the result of interactions between the genetic potential of the fetus and the intrauterine environment to which it is exposed. Animal breeders have long acknowledged the presence of environmental effects (Lush, 1937) and have generally attributed them to intrauterine and post-natal factors inherent to the mother and extra-chromosomal inheritance (Meyer, 1992). These non-genetic maternal effects are viewed as the means by which the mother transfers information about the environment to the offspring, thereby enhancing the offspring's adaptation to its future environment. Lately, in sheep, considerable effort has been focused on identifying factors that can alter the maternal intrauterine environment and how these factors interact with the growth potential of the developing fetus (see reviews by Greenwood and Bell, 2003; Greenwood and Thompson, 2007; Gootwine, 2013; Kenyon and Blair, 2014; Bell and Greenwood, 2016).

In sheep, the effect of changes in the ewe nutrition during pregnancy on fetal weight has been extensively summarised in many narrative reviews (Robinson, 1977; Mellor, 1983; Greenwood and Bell, 2003; Luther et al. 2005; Kenyon, 2008; Kenyon and Blair, 2014) and only one meta-analytic review (Gootwine, 2013). Combined, these reviews suggest that undernutrition during early and mid-pregnancy had little influence on fetal weight near term. In contrast, maternal undernutrition during late pregnancy was associated with a decrease in fetal weight near term. Overnutrition studies have mainly focused on adolescent pregnancy outcomes (see review by Wallace et al. 2006), with few adult sheep studies. Gootwine (2013) reported that only long periods of overnutrition (up to 120 days) in adult sheep increased fetal weight near term compared to controls. Current knowledge suggests

that the degree to which fetal weight is affected by maternal nutrition is variable and dependent on various experimental factors. These factors can be divided into three groups: Firstly, study-related factors, which include the type, length, timing and severity of the nutritional manipulation and the nutritional level post the intervention period. Secondly, maternal-related factors, which include breed, age, live weight and condition score. Thirdly, offspring-related factors, which include gestation length, genotype, litter size and sex (Harding and Johnston, 1995; Greenwood and Bell, 2003; Luther et al. 2005; Kenyon and Blair, 2014; Bell and Greenwood, 2016).

Current reviews have provided insights into the factors that influence fetal growth during intrauterine life and their mechanisms but have been limited to narrative summaries often focused on biomedical research (Harding, 2001; Rhind et al. 2001; McMillen and Robinson, 2005; Wu et al. 2006). Estimates from Gootwine's (2013) meta-analysis provided, for the first time, quantitative values based on a combination of both biomedical and agricultural research. However, this meta-analysis does not provide insights about the variation in responses across nutritional experiments and the factors that may be responsible for this variation and thus, there are still four unanswered questions from this meta-analysis: i) what is the variation in the response to under- and overnutrition across studies?; ii) based on this variation, how reliable are the estimates provided in Gootwine's meta-analysis?; iii) can these estimates be generalised for different populations where average fetal weights vary?; and finally, iv) do the estimates of maternal nutrition vary across single and twin pregnancies?.

There have been many developments in meta-analytic methods (see Nakagawa and Santos, 2012) that could provide further insights about the effect of maternal nutrition during pregnancy on LGFW. It is therefore necessary to update the current knowledge and address the above questions to determine an ideal nutritional regimen for the pregnant ewe that can optimise late gestation fetal weight (LGFW). Hence, the present meta-analysis focused specifically on nutritional studies where control animals (either fed at, or above their theoretical pregnancy maintenance (PM) requirements) were compared to treatment groups that were subjected to various nutritional manipulations throughout pregnancy. To compare the mean LGFW from treatment and control groups, Hedges 'g (a measure of effect size; Hedges, 1981, Nakagawa and Cuthill, 2007) was calculated. The aims of this meta-analysis were three-fold. Firstly, to quantify the extent to which experimental variables can influence the magnitude and direction of the effect of maternal nutrition on LGFW. It was hypothesised that maternal undernutrition in late pregnancy would result in lighter fetuses when compared to those from control-fed dams. By contrast, early- and mid-pregnancy undernutrition would have no influences on the weight of the fetus near term. It was also hypothesised that the degree of fetal weight loss due to maternal undernutrition would be larger in twins than in singletons since twin fetuses are already maternally constrained. It was further hypothesised that overnutrition in adult sheep would have only a small positive effect on LGFW, but that any increase in fetal weight would be larger for twins than for singletons. Secondly, to quantify the degree of variation in results (ie. heterogeneity) across the included studies, thereby allowing the assessment of the reliability of our estimates and thirdly, to examine the bias in the literature of maternal nutrition and how this bias could affect the development of feeding guidelines useful for agriculture.

2.3 Material and methods

Meta-analytic reviews must follow a clear set of guidelines if results are to be a true critical assessment of the available literature. The “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” statement (PRISMA; Moher et al. 2009) aims to promote transparency in the process of literature synthesis in the health sciences. Though medically orientated, the PRISMA statement promotes the reporting of a minimum set of elements aiming to improve the reporting quality of systematic reviews and meta-analyses. In addition, it offers a flow diagram that allows visualization of all procedures from literature search until the final data inclusion decisions (Nakagawa and Poulin, 2012). For these reasons, the systematic review and meta-analyses presented here were conducted by adopting the PRISMA statement where possible.

2.3.1 Literature search and selection criteria

The literature search aimed to collect studies published before 1 December 2013 using the databases PubMed, SCOPUS and Web of Knowledge. The search terms included the following key words and truncated words: (sheep OR ovine OR ewe* OR ovis aries) AND (nutri* OR diet* OR *feed* OR *allowance OR "feed allowance" OR IUGR OR periconception* OR peri-implantation) AND (foet* OR fetus OR fetal OR fetal weight OR foetal weight OR gest* OR pregnan* OR prenatal OR maternal) AND (weight OR mass OR growth OR development OR size), without publication date and language restrictions. Potentially relevant studies and key reviews were identified during the initial screening of the retrieved records. These studies were then used to perform further backward (paper cited) and forward (papers citing) searches. The selected primary studies were also re-

assessed for eligibility based on their full text, supplementary materials and information obtained directly from the authors, as relevant.

To be eligible for meta-analysis, a study had to fulfil a set of eligibility criteria, defined *a priori*, and that had previously been subjected to consensus between the meta-analysis authors. The main criteria for study inclusion were: 1) experiments conducted in adult, multiparous sheep, 2) sheep breed had to be stated in the text, 3) clear reported information on maternal nutritional manipulations during pregnancy (periconceptual and flushing periods included), and 4) fetal weight data collected later than 100 days after conception. A final re-assessment was required to select studies that presented sufficient data to calculate an effect size between a control and a nutritionally-manipulated group. The data that were required included: the number of ewes and fetuses in each treatment, the mean fetal weight for each treatment and their corresponding measurement of dispersion, and whether the study was undertaken in singletons or twins. Studies failing to report the data required to calculate an effect size were excluded and were not used in analyses. Studies reporting the mean fetal weight for singletons and twins together were also excluded. Studies undertaken in twins but reporting only fetal weight for one twin in the set were excluded. Additionally, all studies involving adolescent (7 to 10 months of age at breeding) or nulliparous (first lambing regardless of age) sheep were excluded because evidence suggests that young mothers tend to have lighter and smaller lambs (Corner et al. 2013) and that nulliparous dams often give birth to lighter lambs (Gootwine et al. 2007) compared to their mature counterparts. Finally, review papers, duplicated data and studies in triplet-bearing ewes were also excluded from the data set.

2.3.2 Data extraction and coding

Data were extracted from published article text, tables and graphs. Where needed, GraphClick (Arizona-Software, Los Angeles, CA, USA; Boyle et al. 2013) was used to extract relevant information presented as figures. In studies where essential data were not available (e.g. sample size, fetal weight, litter size or maternal weights), authors were contacted by electronic mail (e-mail). The contacted authors were provided with a brief description of the meta-analysis, complete article citation, the specific information needed for inclusion in the meta-analysis and a request for unpublished data. If adequate data could not be obtained from the authors the study was excluded.

The core data extracted from the final set of studies was coded for analysis and comprised: first author name, year of publication and journal, study ID and experiment ID (sometimes there were more than one independent experiment presented in a single study publication), sample sizes, and the type, duration and timing of nutritional manipulation (i.e. “start day” and “end day” of manipulation) and LGFW. Additional data were collected from each study for use as potential predictors to explain heterogeneity and bias in the data and comprised: litter size, maternal breed, age and, where available, maternal body weight at the start and end of the nutritional manipulation, as well as, prior to parturition, diet fed after the manipulation ended and other relevant information, including comments and requests for data.

In this study, the term “pregnancy maintenance (PM) requirements” is defined as the amount of energy required to maintain ewe net live weight throughout pregnancy, whilst allowing for adequate growth of the fetus at each individual stage of pregnancy. Any

nutritional intervention below and above this threshold is referred to as undernutrition or overnutrition, respectively. The measure of effect size selected for this study was Hedges' g (Hedges, 1981). Hedges' g in the present study represents a standardised difference in LGFW between the experimental group and the control group in terms of the pooled standard deviation, with a small sample size correction (Nakagawa and Cuthill, 2007). A negative value of g represents a lighter fetus in the under- or overfed dams relative to fetuses from control dams, and vice versa. As a general benchmark (Cohen, 1988), the magnitude of an effect can be interpreted as small ($g = 0.2$), moderate ($g = 0.5$) or large ($g = 0.8$).

2.3.3 Statistical analysis

2.3.3.1 Datasets

After the final assessment for study selection, data were split into two main datasets. These two datasets represented the mixture of experiments undertaken by researchers studying the effect of maternal nutrition on LGFW:

1. Undernutrition dataset: Data comparing an experimental group exposed to an undernutrition manipulation to that of a control-fed group. Often, two types of control groups were present in the selected literature: i) a control group fed to their PM requirements (PM-fed) or ii) a control group fed above their predicted PM requirements (usually referred to as well-fed, high-plane or *ad-libitum* control). In some situation, studies were conducted so they had a PM-fed group (used as control), an underfed and an overfed group. In these cases, two comparisons were extracted from these literature: i) PM-fed control vs underfed group, and ii) overfed group vs underfed group. So, to make clear distinction between PM-fed and overfed

controls and to test for differences in the magnitude of effect size estimates due to different control groups (PM-fed vs. overfed), an additional variable was created (i.e. control group: fitted as a binary variable with 1 being PM-fed controls and -1 for overfed controls)

2. Overnutrition dataset: Data comparing an experimental group exposed to varying degrees of overnutrition to that of a control group fed at a pregnancy maintenance level.

These two datasets were analysed independently using meta-analytic and meta-regression models, as described below.

2.3.3.2 Meta-analysis and meta-regression

All statistical analyses were performed using R v.3.0.2 (R Development Core Team, 2013). To analyse the effect sizes and predictors, Bayesian mixed-effect meta-analysis was utilised as implemented in the MCMCglmm package (Hadfield, 2010; Hadfield and Nakagawa, 2010).

For both datasets (undernutrition and overnutrition), model selection was based on the available data and two main models were considered. Model 1 assessed the undernutrition dataset as an intercept-only (null) model (traditional meta-analysis) controlling for maternal breed and study non-independence (i.e. random factors). For the overnutrition dataset, given the small number of studies included for analysis, Model 1 only included experiment as a random factor. These meta-analytic models can be written as (following notation by Gelman and Hill, 2007; Nakagawa and Santos, 2012):

$$g_i = \alpha + s_{j[i]} + b_{k[i]} + e_i + m_i,$$

$$\mathbf{s} \sim N(\mathbf{0}, \sigma_{exp}^2 \mathbf{I}),$$

$$\mathbf{b} \sim N(\mathbf{0}, \sigma_{breed}^2 \mathbf{I}),$$

$$\mathbf{e} \sim N(\mathbf{0}, \sigma_e^2 \mathbf{I}),$$

$$\mathbf{m} \sim N(\mathbf{0}, \mathbf{M}),$$

where g_i is the observed effect-size, α is the overall intercept or meta-analytic mean, $s_{j[i]}$ denotes the experiment-specific effect for the j th experiment ($j = 1, \dots, N_{experiment}$) applied to the i th effect size ($i = 1, \dots, N_{effect-size}$; $N_{effect-size}$ is the number of effect-sizes), \mathbf{s} is a 1 by $N_{experiment}$ vector, which is normally distributed around 0 with the between-experiment variance of σ_{exp}^2 (which was unknown but estimated from the data), $\mathbf{0}$ is a 1 by $N_{experiment}$ vector of 0 and \mathbf{I} is the $N_{experiment}$ by $N_{experiment}$ identity matrix; $b_{k[i]}$ (only used in the undernutrition meta-analysis) is the breed-specific effect for the k th breed ($k = 1, \dots, N_{breed}$; ; N_{breed} is the number of breeds) applied to the i th effect size estimate, and \mathbf{b} is a 1 by vector of b_j , which is normally distributed around 0 with breed-specific variance of σ_{breed}^2 (which was unknown but estimated from the data); e_i is the within-experiment effect for the i th effect-size, and \mathbf{e} is a 1 by $N_{experiment}$ vector of e_j , which is normally distributed around 0 with the within-experiment variance of σ_e^2 (which was unknown but estimated from the data). Lastly, m_i is the sampling error effect for the i th effect-size, \mathbf{m} is a 1 by $N_{experiment}$ vector of m_j , which is normally distributed around 0 with the typical sampling error variance of σ_m^2 (see details in “heterogeneity” section as to how this was estimated), and \mathbf{M} is a $N_{experiment}$ by $N_{experiment}$ matrix, with its diagonal elements being σ_m^2 , which is assumed to be known.

Model 2, the meta-regression, was equivalent to Model 1 in each dataset with the following potential predictors added: i) control type (i.e. undernutrition dataset only) and ii) litter size (both predictors coded as binary variables with category 1 assigned for singletons or PM-fed controls and category -1 for twins or well-fed controls), iii) day when the nutritional manipulation ended and iv) duration of the nutritional manipulation. Meta-regression model in the present study were given by:

$$g_i = \theta_i + s_{j[i]} + b_{k[i]} + e_i + m_i,$$

$$\theta_i = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} \dots \beta_n x_{nj},$$

where β_0 is the intercept, $\beta_{1\dots n}$ are regression coefficients and represent the change in effect-size for unit increase in x , with $x_{1\dots n}$ being the values for the predictor variables (where $j = 1 \dots N_{\text{experiment}}$).

All continuous moderators were Z-scaled (i.e. mean-centred and scaled by sample standard deviation, SD) and, therefore, their regression coefficients need to be interpreted as the amount of change in effect size when the moderator value changes by one standard deviation. For each model, information on posterior mode, mean, standard deviation and 95% highest posterior density (HPD) intervals for meta-analytic model's intercepts and moderator slopes was collected. The posterior mean is reported as the point estimate of the meta-analysis. The estimates were considered statistically different from zero only if the 95% HPD intervals did not include zero.

Three independent Markov Chain Monte Carlo chains were run for each model. Each chain was run for 130,000,000 iterations with a thinning of 1,000,000 after 30,000,000 iterations of burn-in. Random effects for all models were run with the expanded parameter inverse-Wishart prior (the parameter settings in *MCMCglmm* are: $V = 1$, $nu = 0.002$, $alpha.mu = 0$, $alpha.V = 1000$), whilst we used the default prior (a diffused non-informative prior) for fixed effects. Model convergence and mixing were assessed using the Gelman-Rubin statistic (Gelman and Rubin, 1992) and autocorrelation within chains, respectively. Chain selection was performed by choosing the chain with the lowest deviance information criterion (DIC, Spiegelhalter et al. 2002). Correlated structures arising from shared control group identities were taken into account by estimating the variance-covariance matrix of the shared identities and including them in the models.

2.3.3.3 *Assessment of heterogeneity*

Heterogeneity of results among studies was estimated by calculating a modified version of the I^2 statistic proposed by Higgins and Thompson (2002) which is suitable for multilevel meta-analytic models (Nakagawa and Santos, 2012), where the percentage of variance at each random effect is considered in relation to the sum of all variance components. In this study, total variance is defined by:

$$\sigma_t^2 = \sigma_{exp}^2 + \sigma_{breed}^2 + \sigma_e^2 + \sigma_m^2$$

where σ_{exp}^2 is the experiment-level variance, σ_{breed}^2 is the dam breed-level variance (i.e. only for models using breed as random effect). Otherwise $\sigma_t^2 = \sigma_{exp}^2 + \sigma_e^2 + \sigma_m^2$, σ_e^2 is the residual variance and σ_m^2 is what is referred to as the typical sampling error variance, which can be defined as (Higgins and Thompson, 2002):

$$\sigma_m^2 = \frac{\sum_{i=1}^k w_i(k-1)}{(\sum_{i=1}^k w)^2 - \sum_{i=1}^k w_i^2}$$

where w_i is the inverse of the i th measurement error variance associated with the i th g estimate ($i = 1, \dots, k$). Therefore, the proportion of experiment-level and dam breed-level variance in relation to the total sum of variance components is $\sigma_{exp}^2/\sigma_t^2$ and is $\sigma_{breed}^2/\sigma_t^2$, respectively. Total heterogeneity was calculated as:

$$I^2 = \frac{\sigma_t^2 - \sigma_m^2}{\sigma_t^2} \times 100$$

The I^2 statistic describes the amount of total variation across studies (percentage), which is due to heterogeneity (variability in results) rather than by chance. I^2 values of around 25, 50 and 75% are considered as low, medium and high heterogeneity, respectively (Higgins et al. 2003).

2.3.3.4 R^2 estimation for meta-regression models

To determine the contribution of fixed and random effects explaining variation in the responses across studies in the meta-regression models, two R^2 statistics were calculated, as suggested by Nakagawa and Schielzeth (2013). The marginal R^2 measures the variance explained by the fixed effects as a proportion of the sum of all variance components and was defined as:

$$R_{LMM(m)}^2 = \frac{\sigma_f^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

where σ_f^2 is the variance attributable to the fixed effects, σ_l^2 is the variance component of the l th random factor, σ_e^2 , is the residual variance. Note that σ_m^2 is not part of the formula, as it is considered to be explained already. In addition, the variance explained by fixed and

random factors (i.e. conditional R^2) was calculated by integrating into the numerator the variance explained by the random factors:

$$R_{LMM(c)}^2 = \frac{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

2.3.3.5 *Publication bias*

Publication bias may result from statistically non-significant results being less likely to be published than results showing large effects (Rothstein et al. 2005). In the present study, publication bias was investigated both graphically, by visual inspection of funnel plots for the presence of data distribution asymmetry (Rothstein et al. 2005) and statistically, by formal testing of funnel plot asymmetry using a modification of Egger's regression (Egger et al. 1997) applied to the sum of the residual and sampling errors effects from the full models (Nakagawa and Santos, 2012).

2.3.3.6 *Sensitivity analysis*

Given that most studies in this meta-analysis had sample sizes of less than 20 fetuses per group, it is possible that by using Hedges' g as the effect size metric, the sample standard deviation may have been estimated poorly. As a result, the natural logarithm of the Response Ratio (lnRR) was chosen as an alternative effect size, as it is more suitable for meta-analysis when sample sizes are small (Hedges et al. 1999; Lajeunesse, 2011). As a consequence, each meta-analytic and meta-regression models were re-run with the lnRR as an alternative effect size.

2.4 Results

2.4.1 Study retrieval and selection strategy

The course of the systematic review is illustrated in the flow diagram following the PRISMA statement (Figure 9). The initial electronic search identified 2729 potentially relevant citations. An additional 232 references were identified after examining key reviews and other sources. After title, abstract and occasional full-text scan, 2689 studies were excluded because they were irrelevant to the research question. The remaining 265 studies were identified as potentially relevant studies and were examined in detail. Of these, 210 studies did not meet the inclusion criteria and were excluded from this study (Figure 1, see also 2.8.1 Supplementary references -list of excluded studies). Authors were contacted for additional information related to 29 studies and written clarification for 24 studies was received. However, no unpublished or other relevant data were obtained. The initial database consisted of 95 effect sizes extracted from 55 studies (2.8.2 Supplementary references – list of included studies) and they represented two major experimental set-ups: relative undernutrition and relative overnutrition. In some cases, studies reported both experimental set-ups.

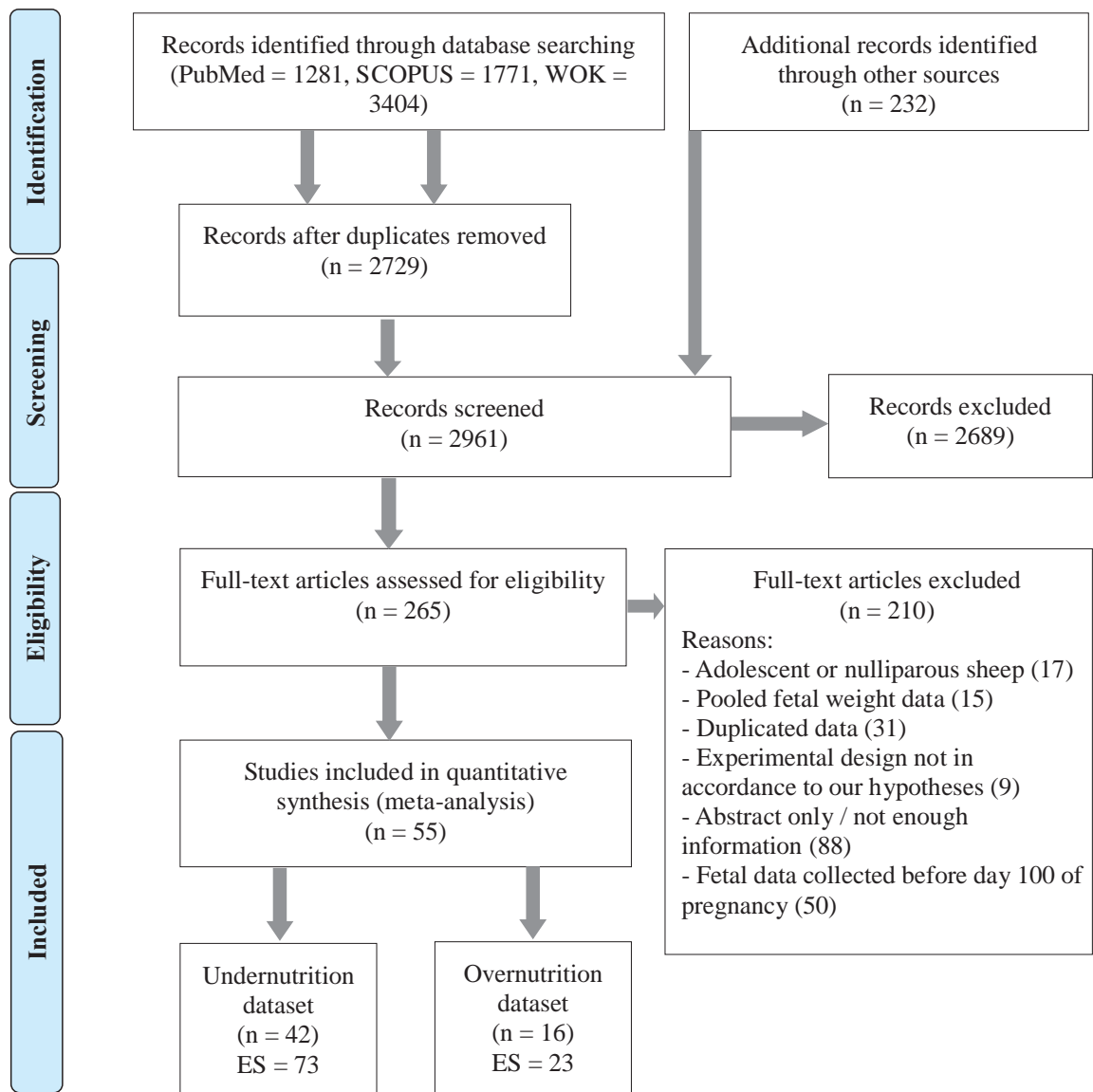


Figure 9. A Preferred Reporting Items for systematic Reviews and Meta-Analysis (PRISMA) flow diagram. The number of studies in each particular category is shown in parenthesis. The number of effect sizes (ES) is shown for each dataset.

2.4.3 Undernutrition

The undernutrition dataset consisted of 42 studies involving 44 different experiments. These experiments were conducted in 8 countries, using 10 different sheep breeds. Seventy-three effect sizes were extracted from this literature and were used for meta-analysis. In general, there was a wide variation in nutritional manipulations. These manipulations started between 89 days before conception and 120 day into pregnancy (with mean and standard deviation (SD) = 24 ± 59). Similarly, nutritional manipulations finished between day 6 and 147 of pregnancy (with mean and SD of 86 ± 43). These nutritional manipulations lasted, on average, 62 days (SD = 43) and ranged between 10 and 222 days. Thirteen studies did not have information regarding the level of undernutrition and/or did not have enough data for the exact level of undernutrition to be estimated. The remaining studies reported undernutrition levels that ranged between 30% and 80% the PM requirements; with the most common undernutrition level being 50% PM (38% of all extracted ES).

In general, maternal undernutrition during pregnancy resulted in a non-significant overall effect on LGFW ($\beta_{[\text{meta-analytic mean}]} = -0.39$, 95% HPD = -0.80 to 0.05; see Supplementary Table S2.1). This initial analysis also revealed moderate heterogeneity among effect sizes ($I^2_{\text{total}} = 55.80\%$, $I^2_{\text{between-experiments}} = 4.80\%$, $I^2_{\text{between-breeds}} = 47.40\%$ and $I^2_{\text{residual}} = 3.60\%$) thereby suggesting that additional unidentified factors were responsible for variation in the observed results. The timing (i.e. the stage of pregnancy when nutritional manipulations ended) and duration of nutritional manipulations were identified as the factors that better explained the variation in LGFW responses across studies. In terms of timing, there was a negative effect that became more apparent as pregnancy progressed. Results from the meta-

regression (see Supplementary Table S2.1) revealed that responses to nutritional manipulations ending in early- and mid-pregnancy were somehow variable in magnitude and direction but represented non-significant effects on LGFW ($\beta_{[\text{Early-pregnancy}]} = -0.0007$, 95% HPD = -0.36 to 0.34; $\beta_{[\text{Mid-pregnancy}]} = -0.02$, 95% HPD = -0.36 to 0.33, Figure 10). In contrast, nutritional manipulations during late-pregnancy or that extended into late-pregnancy consistently resulted in lighter fetuses compared to controls ($\beta_{[\text{Late-pregnancy}]} = -0.79$, 95% HPD = -1.09 to -0.47). The negative effect of undernutrition was intensified as nutritional manipulations increased in length ($\beta_{[\text{total days of manipulation}]} = -0.16$, 95% HPD = -0.31 to -0.03, Figure 10).

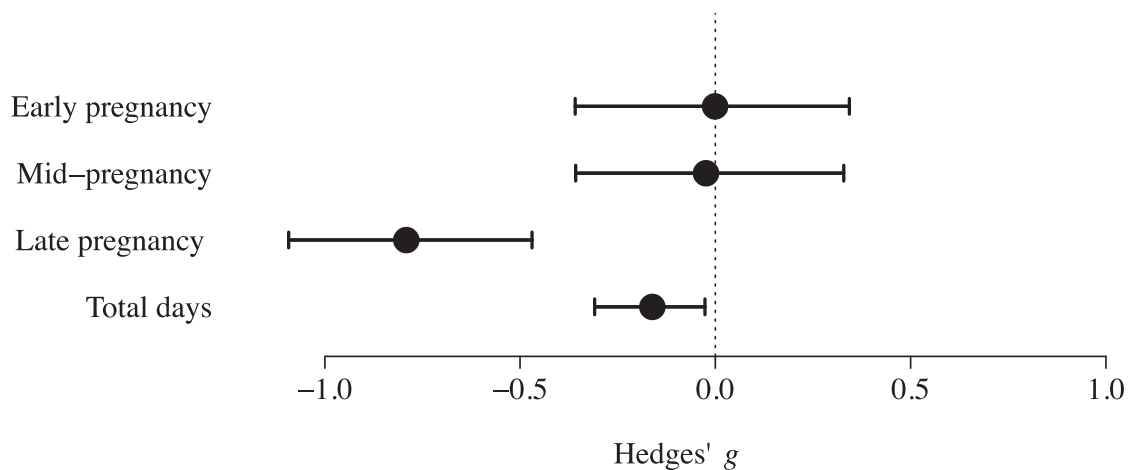


Figure 10. Forest plot of estimates from the meta-regression of the undernutrition dataset. Posterior means for each period of pregnancy (intercepts) and “total days” (slope) are represented by circles. Horizontal lines represent 95% highest posterior density (HDP) intervals. Zero effect is shown as a vertical dashed line. Statistically significant effects are considered those whose 95% HDP do not cross zero.

There were marginal differences in effect size estimates between singleton and twins or between the types of control used in the experiments (ie. PM-fed or overfed). These differences, however, were not significant. Inclusion of these predictors did not increase the variation explained by the fixed effects or the full model and therefore were excluded from the main analysis. These analyses are presented in the supplementary material (Supplementary Table S2.2).

In this dataset most of the variation among effect sizes resided at the dam breed level ($I^2_{\text{between-breeds}} = 47.40\%$). The inclusion of timing and length as predictors resulted in a 71% decrease in the variance allocated to breed, thereby suggesting that breed and most likely, timing, were confounded by experimental design (i.e. a particular breed used to study only one period of pregnancy). Yet, most of the variation in the data was explained by the full model ($R^2_{\text{LMM}(c)} = 97\%$), with much of this variation explained by only two predictors ($R^2_{\text{LMM}(m)} = 57\%$).

To better understand how the timing of undernutrition affected LGFW, subgroup analyses were conducted. The study characteristics of each subgroup are presented in Table 3 and the individual results from each subgroup are shown in Supplementary Tables S2.3, S2.4 and S2.5. These results showed that heterogeneity within each subgroup was relatively low ($I^2_{\text{total [early-pregnancy]}} = 25.80\%$, $I^2_{\text{total [mid-pregnancy]}} = 33.80\%$, $I^2_{\text{total [late-pregnancy]}} = 20.10\%$) thus confirming that much of the variation in results seen in the undernutrition dataset was due to differences in the timing of nutritional manipulations. In addition, this analysis also confirmed previous findings that nutritional manipulations ending in early to mid-pregnancy resulted in variable fetal weight responses (positive and negative), whilst those

ending in late-pregnancy consistently affected fetal weight. However, this subgroup analysis revealed that within the early- and mid-pregnancy subgroup, other experimental variables were responsible for the difference in result. In the early-pregnancy subgroup, some of the variation in results resulted from differences in the day when fetal weight was measured and the duration of the nutritional manipulations. Studies that measured fetal weight beyond day 130 of pregnancy consistently found a negative effect on fetal weight, whilst those measuring fetal weight before day 135 resulted in more variable responses. Similarly, nutritional manipulations lasting for longer than 60 days were more likely to find a negative effect, which coincided with most “periconceptual” undernutrition studies where nutritional manipulations lasted around 90 days or more.

Table 3. Main characteristics of the nutritional restrictions of the three undernutrition subgroups (early-, mid- and late-pregnancy).

Description	Undernutrition subgroup*		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
No. of studies per subgroup	13	18	19
No. of experiments per subgroup	14	18	20
No. of effect sizes per subgroup	19	21	33
Start of restriction (day post-conception)			
Mean (\pm SD [†])	-30 \pm 34	19 \pm 17	57 \pm 64
Range	-60 – 26	-14 – 46	-89 – 120
End of restriction (days post-conception)			
Mean (\pm SD)	29 \pm 12	78 \pm 11	127 \pm 14
Range	6 – 50	65 – 96	107 – 147
Duration of restriction (days)			
Mean (\pm SD)	59 \pm 29	59 \pm 15	70 \pm 65
Range	19 – 90	34 – 84	10 – 222
Outcome day (days post-conception)			
Mean (\pm SD)	130 \pm 9	132 \pm 11	130 \pm 14
Range	110 – 143	110 – 145	107 – 147

* Refers to studies ending within each stage of pregnancy; [†] standard deviation

The mid-pregnancy subgroup was characterised by nutritional regimes that, on average, resulted in a small but positive but non-significant effect on LGFW. The size and direction of these effects across studies appeared to have been driven by when fetal weight was measured and how close to day 100 of pregnancy the nutritional manipulation lasted. In many cases, the largest positive effects (i.e. $d > 0.5$) were found in studies ($n = 6$) that measured fetal weight between day 110 and 129 of pregnancy with nutritional manipulations that finished around day 70 of pregnancy. Further, there were only a few studies showing noticeable negative effects ($n = 2$; $d < -0.5$) with nutritional manipulation lasting up to day 96 of pregnancy and that measured fetal weight around day 141.

2.4.4 Overnutrition

Only 16 studies involving 16 experiments involving overnutrition were deemed acceptable for quantitative analysis. A total of 22 effect sizes were extracted from these studies. The extracted data were representative of variations in the duration of the nutritional manipulations rather than overnutrition at specific stages of pregnancy. The most common overnutrition levels were 50% above PM requirements and *ad-libitum* feeding (43% and 38% of all extracted ES, respectively). Across studies, the duration of overnutrition ranged between 25 to 245 days (with mean and SD = 123 ± 72). Fetal weight measurements were taken between day 100 and 143 of gestation (135 ± 9).

Overall, maternal overnutrition had no significant effect on fetal weight ($\beta_{[\text{meta-analytic mean}]} = 0.13$, 95% HPD = -0.20 to 0.45). Moderate heterogeneity was noted in this dataset ($I^2_{\text{total}} = 51.60\%$), which justified further exploration of predictors. The magnitude of fetal weight responses to overnutrition appeared to be controlled, to some extent, by litter size ($\beta_{[\text{singletons}]}$)

= 0.54, 95% HPD = 0.02 to 1.10; $\beta_{[\text{twins}]} = -0.03$, 95% HPD = -0.34 to 0.35) and the duration of the nutritional manipulations ($\beta_{[\text{twins}]} = -0.18$, 95% HPD = -0.42 to 0.07; see also Figure 11). Singleton fetuses benefited from maternal overnutrition and were heavier than their control counterparts, except when overnutrition lasted for 245 days. On the contrary, twin fetuses had more variable responses (positive and negative), with negative effects mainly being the result of long-term overnutrition (i.e. more than 120 days) and positive effect recorded in studies with nutritional manipulations that mostly lasted between 29 and 120 days.

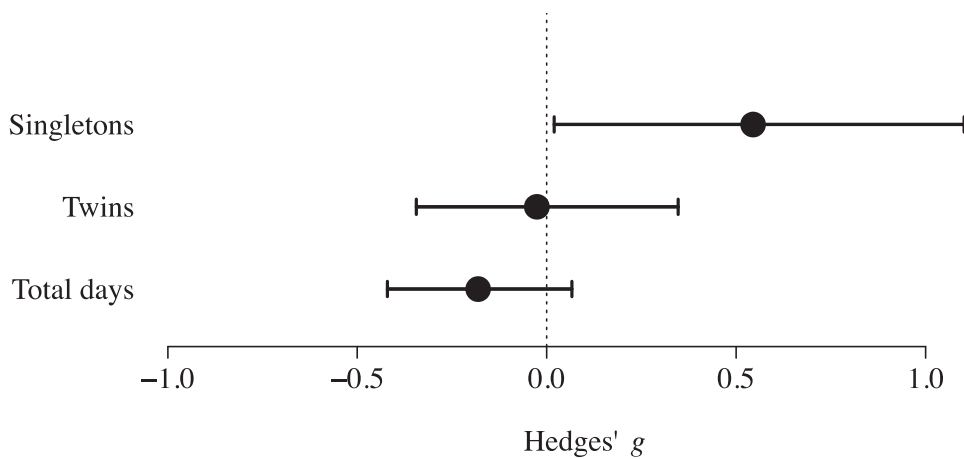


Figure 11. Forest plot of estimates from the meta-regression of the overnutrition dataset. Posterior means for each litter size (intercepts) and “total days” (slope) are represented by circles. Horizontal lines represent 95% highest posterior density (HDP) intervals. Zero effect is shown as a vertical dashed line. Statistically significant effects are considered those whose 95% HDP do not cross zero.

Much of the variation in study outcomes was attributed to differences between experiments ($I^2_{\text{between-experiments}} = 42.10\%$, $I^2_{\text{residual}} = 9.60\%$). Including litter size and the duration of overnutrition as predictors in the meta-regression resulted in a $R^2_{\text{GLMM}(m)}$ of 39%, thereby

reducing the variance at the experiment level by 43%. (Supplementary Table S2.6). The residual variance was relatively unaffected by the inclusion of the predictors.

2.4.5 Publication bias

There was little evidence of publication bias in this meta-analysis. Visual inspection of funnels plots in the undernutrition (Figure 12a and Figure 12b) and overnutrition (Figure 12c and Figure 12d) datasets indicated no sign of data distribution asymmetry. These results were confirmed by non-statistically significant intercepts obtained using Egger's regression approach on the meta-regression residuals ($\beta_{[\text{intercept} - \text{UN dataset}]} = 0.45\%$ HPD = -0.34 to 1.23; $\beta_{[\text{intercept} - \text{ON dataset}]} = -0.34$, 95% HPD = -2.08 to 1.76).

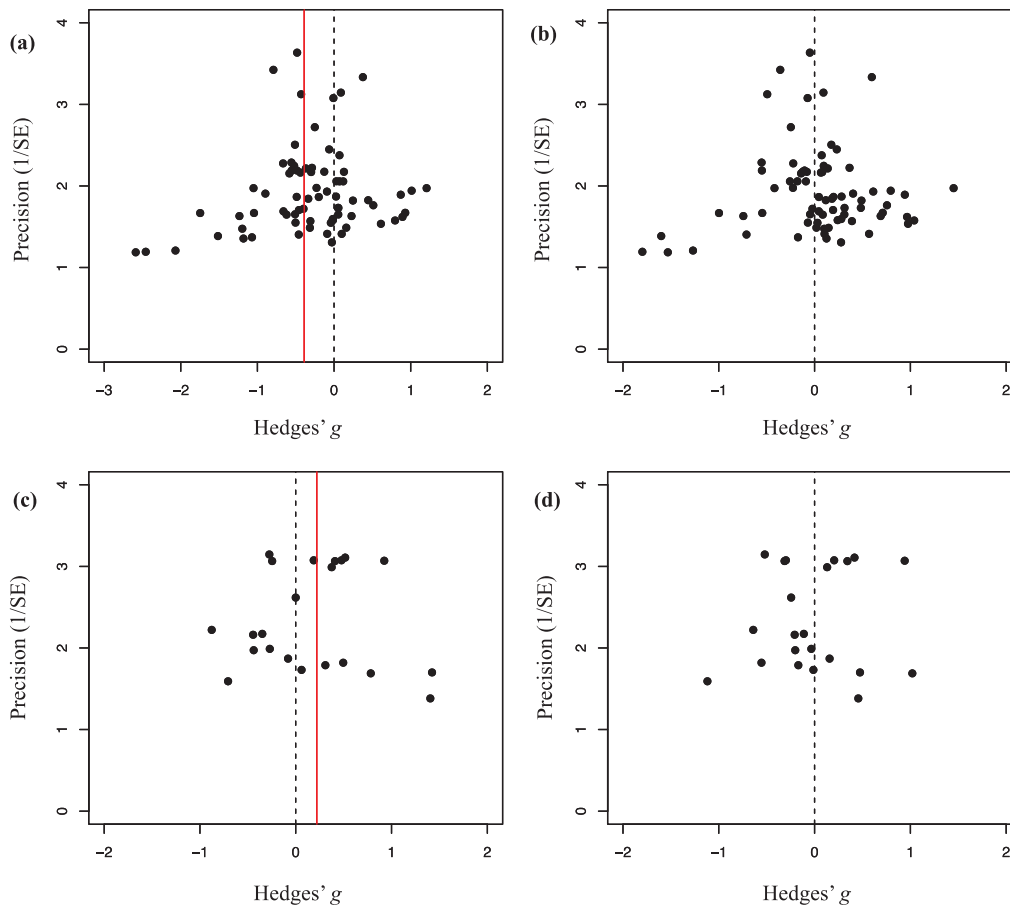


Figure 12. Funnel plots of raw data (a and c) and the residuals and sampling error effects (b and d) from full models in the undernutrition (a and b) and overnutrition (c and d) datasets. Overall posterior (meta-analytic) means are shown as solid lines and zero effect sizes are shown as dashed lines.

2.4.6 Sensitivity analysis: $\ln RR$ as an alternative effect size

The results from the meta-analysis using the log response ratio ($\ln RR$) supported the previous results from the main analysis (using Hedges' g), as it showed a similar pattern of statistical results in every dataset (Supplementary Tables S2.7 – S2.11). However, and contrary to the main analysis, this sensitivity analysis also revealed high heterogeneity ($I^2_{\text{total}} = 75\%$) in the undernutrition dataset, with moderate heterogeneity remaining after the

dataset was split in subgroups ($I^2_{\text{total [early-pregnancy]}} = 41\%$, $I^2_{\text{total [mid-pregnancy]}} = 51\%$, $I^2_{\text{total [late-pregnancy]}} = 60\%$). In addition, inclusion of predictors in the meta-regression models for each subgroup was only able to explain between 10% and 36% of the variation in the data, as compared to the main analysis (using Hedges' g) where the same predictors explain between 40% and 64% of the variation in the data. This suggests the possibility of underestimation of the variation in the data using Hedges' g . This could in part be due to small sample sizes across studies, which at an average of 10 fetuses per experimental treatment, was relative low.

2.5 Discussion

Although late gestation fetal weight is not an agriculturally relevant trait, the development of the fetus during late-pregnancy determines its weight at birth (Robinson et al. 1977) and thus LGFW is of interest as an indicator of effects that maternal nutrition may ultimately have on lamb birth weight. Therefore, this meta-analysis sought to examine the effect of varying maternal nutrition during pregnancy on LGFW and its implications in sheep production. Maternal undernutrition studies showed varying effects on LGFW. This variation in study findings was best explained by the timing and duration of the nutritional manipulations. Undernutrition during early and mid-pregnancy appeared to generate inconsistent and opposing LGFW responses, resulting in non-significant intercepts. On the contrary, nutritional manipulations during late-pregnancy or those that extended into late-pregnancy were associated with the greatest decrease in LGFW. Furthermore, short-term maternal overnutrition showed a general trend towards a small increase in LGFW. However, this effect disappeared or became negative as nutritional manipulations extended beyond 120 days. Moderate heterogeneity was observed across under- and overnutrition

studies. However, this inconsistency in responses across studies was reduced once different experimental variables were accounted for. Publication bias did not affect the results from this meta-analysis. Yet, the analysis of the aggregated data from all trials may be limited by the amount of information that could be obtained either from published literature or directly from authors. It was also noted that a large number of studies had to be excluded, due largely to a lack of published detail, which can affect the meta-analysis in the absence of publication bias.

This meta-analysis highlighted the importance of managing the ewe nutrition in late-pregnancy as a means to achieve optimum LGFW. The findings suggested that maternal nutritional restriction from mid-to-late and late-pregnancy would reduce LGFW by up to 1.0 kg, depending on the severity and length of the nutritional restrictions (assuming the mean and calculated SD fetal weight of untreated controls presented by Gootwine (2013) of 4.19 ± 0.97). The available research focuses on a mix of nutritional restriction levels but had predominantly used a reduction in intake equivalent to 50% of pregnancy maintenance requirements. The nature of the data included in this meta-analysis prevented the estimates from being representative of less severe nutritional restrictions such as those often experienced under pastoral conditions due to naturally occurring seasonal changes and further examination is required. However, it does emphasize that reasonably significant nutritional restrictions are needed to affect LGFW when adult ewes have been adequately fed during the first 100 days of pregnancy (which is an indication that ewes entered late-pregnancy on reasonably good condition). In addition, it was found that extending the ewe's nutritional restriction beyond 70 days (thus suggesting that ewe body reserves were affected) would result in a further decrease in fetal weight between 0.01 kg to 0.58 kg,

depending on the length of the restriction. Thus suggesting that ewe body condition may be critical in determining fetal weight responses to maternal undernutrition in late pregnancy. With a lack of individual data on important factors like ewe body weights and BCS at conception and at key time points throughout pregnancy (ie. before and after nutritional manipulations), it is not possible to further investigate and quantify how changes in ewe body weight and BCS affect the magnitude and direction of LGFW responses to late-pregnancy undernutrition. Nevertheless, it is clear that matching the ewe's intake to their theoretical pregnancy maintenance requirements in late-pregnancy will result in optimal growth of the fetus before lambing. These results support the initial hypotheses and are in accordance with previous reviews (Mellor, 1983; Luther et al. 2005; Caton and Hess, 2010; Gootwine, 2013; Kenyon and Blair, 2014).

This meta-analysis detected inconsistent and non-significant effects of early- and mid-pregnancy maternal undernutrition on LGFW. Closer examination of the 31 studies included in this meta-analysis that considered nutritional manipulations ending within the first 100 days of pregnancy, revealed no clear pattern in the data, with both positive and negative effects on LGFW observed. To some extent, it appears that the inconsistency in research findings was mainly due to a high rate of non-replication. Nevertheless, where some replication occurred, as for periconceptual undernutrition studies, consistently small to moderate negative effects on LGFW were found, unless fetal weight was measured before day 130 of pregnancy. Similarly, studies examining undernutrition between day 28 and 80 of pregnancy showed no significant effect on LGFW.

Studies with maternal undernutrition from conception to day 70 of pregnancy found small to large positive effects on LGFW. These latter results are rather interesting for an agricultural perspective because it suggests that it may be possible to decrease herbage demand whilst potentially maximizing the performance of the lamb. However, these results are overshadowed by the low sample sizes in those studies. A possible reason for the increase in LGFW may be that undernutrition around the implantation period (which in sheep occurs between day ~16 and ~20 of pregnancy, Spencer et al. 2004) appears to increase fetal placental vascularization as an adaptive process to increase the transfer of nutrients to the fetus, thereby maintaining fetal growth under anticipated poor nutritional conditions (Steyn et al. 2001). It is possible that this increased capacity for nutrient transfer to the fetus continues after “normal” feeding is resumed, thereby resulting in an increase in LGFW compared to controls. Despite the inconsistent LGFW results of nutritional manipulations in the first 100 days of pregnancy, these studies have highlighted other physiological and developmental effects that could impact the lamb’s later life. Currently, however, the number of available trials and their sample sizes are too low for definitive conclusions as to whether nutritional manipulations would increase or decrease LGFW. Whilst some studies are promising, larger trials are required if they are to be applicable for on-farm advice.

This meta-analysis showed that the estimated LGFW effect sizes for maternal undernutrition were similar for both singletons and twins. Robinson et al. (1977) indicated that regardless of litter size, it is estimated that a fetus obtains approximately 85%, 50% and 25% of their final birth weight in the last 2, 4 and 8 weeks of gestation, respectively. Since the proportion of final weight attained at each specific stage is similar for both singletons

and twins, it is therefore not surprising that the degree to which LGFW is affected by maternal undernutrition is also similar. It is likely, however, that whilst a decrease in LGFW may be tolerable for a singleton, a similar absolute decrease in LGFW for twins may be more detrimental to their survival (Oldham et al. 2011). The combined results from the undernutrition dataset support the recommendation that singleton- and twin-bearing ewes should be managed separately to cater to their specific requirements, especially in late-pregnancy. A major issue with multiple-bearing ewes is that they may fail to consume their nutritional requirements during late pregnancy even when offered adequate pasture allowances and especially in the presence of poor pasture quality. In cases such as this, ewes often utilize their own body reserves to meet their nutritional requirements, thus our results highlight the importance of the nutritional management of twin-bearing ewe post-scanning. It is essential that multiple bearing ewes are fed to meet their theoretical pregnancy requirements prior to late-pregnancy, giving them adequate body reserves to use as a “buffer” if undernutrition is experienced in late pregnancy, thereby potentially lessening any negative impact on fetal growth.

The level of maternal undernutrition is unquestionably an important predictor of changes in LGFW. Given the result from the sensitivity analysis, which showed moderate heterogeneity remaining in the undernutrition subgroups, the level of undernutrition may have played a large role in further explaining the variation in the data that was unaccounted for in this meta-analysis. From a pastoral agriculture perspective, farms can experience many different combinations of length and severity of undernutrition, with farmers often having no knowledge as to how severe the undernutrition actually is. Therefore, by taking into account a broader range of nutritional regimens varying in the level of undernutrition,

whilst allowing for changes in the duration of undernutrition, our estimates are more representative of the many possible scenarios that farmers could experience and thus there is potential for nutritional advice to be tailored to particular scenarios.

Finally, this meta-analysis also showed that overnutrition of adult multiparous sheep during pregnancy resulted in a moderate increase in LGFW in singleton but not in twin fetuses. Whilst increasing fetal weight close to term through maternal nutrition may be desirable in multiple pregnancies from a lamb survival perspective (Oldham et al. 2011), this is not the case for single pregnancies where promoting additional gains in LGFW, and thus birth weight, whilst increasing the ewe condition at lambing may lead to increased mortality rates due to dystocia (McHugh et al. 2016). This litter-specific finding is likely due to the greater uterine constraint in twin pregnancies (Gardner et al. 2007), which limits the opportunity of twin fetuses to increase their LGFW. Recent data suggests that the fetal growth trajectory of twins is largely determined in early pregnancy (Hanckock et al. 2012) and attempts to increase LGFW in twins via above pregnancy maintenance maternal nutrition are largely unsuccessful due to limited placental and uterine capacity. Above pregnancy maintenance nutrition is more likely to influence maternal weight gain rather than fetal growth (see review by Kenyon and Blair, 2014). It is not yet completely clear whether long periods of overnutrition (i.e., more than 120 days) in adult ewes have a detrimental effect on LGFW. The evidence presented in this meta-analysis suggests that there is no increase in late gestation fetal weight when feeding dams above pregnancy maintenance for long periods during pregnancy. It also suggests that overnutrition may be inefficient in the short term given the small increase in LGFW seen across studies, which may be of little importance for agriculture. However, if it has flow on effects in terms of

dam milk production and future breeding performance, short-term overnutrition may be warranted.

Three additional points arising from this meta-analysis require further consideration. Firstly, twenty-one studies had to be excluded due to reporting issues, which restricted their use for meta-analysis. These reporting issues were mainly related to the lack of reporting of specific sample sizes or clear indication of litter size. Whilst this meta-analysis was not affected by publication bias, the number of existing studies and those used for meta-analysis is clearly in mismatch, which could affect the estimation of overall effects. Secondly, many factors are responsible for the magnitude of fetal weight responses to maternal undernutrition, such as experimental, maternal and offspring-related factors. However, these factors are rarely reported in published studies. For example, 23 studies did not report maternal body weight and BCS at any point during the trial. Only 12 studies reported both body weight and BCS measurements before and after the nutritional treatments, and only 20 reported one of these two measurements, mostly maternal body weight. This missing information limits the assessment of the efficacy of treatments and therefore the quality of studies. It also restricts further investigation of the role of these factors in the response variable (LGFW). Thirdly, the difference in effect size between singletons and twins in the overnutrition datasets requires further investigation. It is clear from the analysis that short- and long-term maternal overnutrition have contrasting effects. The limited data obtained for the overnutrition dataset prevented further estimation of the interaction between litter size and the duration of overnutrition.

2.6 Conclusion

This meta-analysis demonstrated that correct management of the ewe nutrition during late pregnancy is essential to achieve optimum fetal weight prior to lambing. Nutritional restriction in late pregnancy significantly decreased LGFW, especially in ewes experiencing long-periods of undernutrition extending into late-pregnancy. Larger trials are required to better elucidate the long-term effects of maternal undernutrition during early- and mid-pregnancy as results from the current pool of studies are varied in magnitude and direction. This meta-analysis showed that increasing LGFW by means of maternal overnutrition may be difficult to achieve in multiple-bearing ewes. More research and more precise reporting of experimental details are needed to further our understanding of the interaction between the timing and duration of overnutrition and to determine whether there are any practical implications for multiple-bearing ewes. Not only in terms of fetal development but also in relation to lamb survival, and the future milk production and breeding performance of the ewe. The majority of studies included in this meta-analysis reported the effects of maternal nutrition on fetal weight but failed to provide adequate detail as to the effect of the nutritional treatments on the ewes themselves. This highlights the importance of reporting outcomes related to all experimental units as such information could help assess the efficacy of treatments. This would provide quality criteria for future meta-analyses but could also further our understanding on how changes in maternal body weight and BCS influence the responses to nutritional manipulations in both the ewe and the fetus. Finally, whilst LGFW may give an indication of potential effects on lamb birth weight, to date there is no meta-analysis quantifying the effect of maternal pregnancy nutrition on lamb birth that would allow comparison of the estimated effect.

2.7 References

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2.8 Supplementary material for Chapter 2

2.8.1 Supplementary references -list of excluded studies

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Pooled fetal weight data for various litter types

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2.8.3 Supplementary tables

Table S2.1 Summary of the statistical results of meta-analytic and meta-regression models in the undernutrition dataset.

Description	Undernutrition models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.39 [-0.80 – 0.05]	-
Early-pregnancy	–	-0.0007 [-0.36 – 0.34]
Mid-pregnancy	–	-0.02 [-0.36 – 0.33]
Late-pregnancy	–	-0.79 [-1.09 – -0.47]
Total days		-0.16 [-0.31 – -0.03]
Random effects	VC	VC
Experiment	0.030	0.024
Breed	0.389	0.111
Residual	0.021	0.009
PCV _[Experiment]	–	20%
PCV _[Breed]	–	71%
PCV _[Residual]	–	57%
$R^2_{LMM(m)}$		57.16%
$R^2_{LMM(c)}$		97.24%
DIC	-122.91	-162.29

VC, variance components; PCV, proportion change in variance; DIC, deviance information.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.2 Summary of the statistical results of the additional meta-regression models in the undernutrition dataset. Litter size and control group type were fitted as additional predictors.

Description	Additional predictors in the undernutrition dataset	
	Litter size	Control group type
Fixed effects	β [95% HPD]	β [95% HPD]
Early-pregnancy	-0.01 [-0.41 – 0.32]	-0.01 [-0.39 – 0.37]
Mid-pregnancy	-0.04 [-0.40 – 0.28]	-0.03 [-0.37 – 0.30]
Late-pregnancy	-0.84 [-1.17 – -0.54]	-0.81 [-1.13 – -0.48]
Total days	-0.15 [-0.30 – 0.002]	-0.15 [-0.30 – -0.008]
Additional predictor	0.08 [-0.09 – 0.25]	0.03 [-0.12 – 0.20]
Random effects	VC	VC
Experiment	0.020	0.026
Breed	0.118	0.128
Residual	0.008	0.008
$R^2_{LMM(m)}$	58.04%	54.78%
$R^2_{LMM(c)}$	97.61%	97.56%
DIC	-161.90	-161.70

VC, variance components; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.3 Summary of the statistical results from the early-pregnancy subgroup analysis.

Description	Early-pregnancy subgroup models		
	Meta-analysis	Meta-regression #1	Meta-regression #2
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	-0.008 [-0.27 – 0.21]	-0.006 [-0.27 – 0.26]	-0.009 [-0.24 – 0.23]
Total days	–	-0.17 [-0.41 –0.06]	–
Outcome day	–	–	-0.32 [-0.59 – -0.06]
Random effects	VC	VC	VC
Experiment	0.055	0.061	0.039
Residual	0.021	0.023	0.016
PCV _[Experiment]	–	-10%	29%
PCV _[Residual]	–	-9%	24%
$R^2_{LMM(m)}$	–	26.10%	64.47%
$R^2_{LMM(c)}$	–	79.84%	89.50%
DIC	-37.15	-36.81	-39.11

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.4 Summary of the statistical results from the mid-pregnancy subgroup analysis.

Description	Mid-pregnancy subgroup models		
	Meta-analysis	Meta-regression #1	Meta-regression #2
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	0.14 [-0.14 – 0.45]	0.16 [-0.09 – 0.41]	0.18 [-0.12 – 0.45]
End day of manipulation	–	-0.35 [-0.62 – -0.10]	–
Outcome day	–	–	-0.27 [-0.54 – 0.02]
Random effects	VC	VC	VC
Experiment	0.107	0.042	0.082
Residual	0.043	0.025	0.041
PCV _[Experiment]	–	61%	23%
PCV _[Residual]	–	42%	5%
R ² _{LMM(m)}	–	64.71%	36.92%
R ² _{LMM(c)}	–	86.93%	78.96%
DIC	-31.33	-37.92	-32.12

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.5 Summary of the statistical results from the late-pregnancy subgroup analysis.

Description	Late-pregnancy models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.77 [-1.05 – -0.53]	-0.79 [-1.03 – -0.53]
Total days		-0.23 [-0.48 – -0.01]
Random effects	VC	VC
Experiment	0.092	0.059
Residual	0.018	0.019
PCV _[Experiment]	–	36%
PCV _[Residual]	–	-5%
$R^2_{LMM(m)}$		40.70%
$R^2_{LMM(c)}$		85.66%
DIC	-65.92	-66.08

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.6 Summary of the statistical results of meta-analytic and meta-regression models in the overnutrition dataset.

Description	Overnutrition models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	0.13 [-0.20 – 0.45]	–
Singletons (intercept)	–	0.54 [0.02 – 1.10]
Twins (intercept)	–	-0.03 [-0.34 – 0.35]
Total days (slope)	–	-0.18 [-0.42 – 0.07]
Random effects	VC	VC
Experiment	0.212	0.120
Residual	0.039	0.039
PCV _[Experiment]	–	43%
PCV _[Residual]	–	0%
R ² _{GLMM(m)}	–	39.34%
R ² _{GLMM(c)}	–	85.04%
DIC	-38.89	-35.59

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.7 Summary of the statistical results of meta-analytic and meta-regression models in the undernutrition datasets using the natural logarithm of the response ratio (lnRR).

Description	Undernutrition models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.04 [-0.09 – 0.004]	-
Early-pregnancy	–	0.01 [-0.03 – 0.07]
Mid-pregnancy	–	-0.0005 [-0.05 – 0.04]
Late-pregnancy	–	-0.10 [-0.14 – -0.06]
Total days		-0.02 [-0.04 – 0.001]
Random effects	VC	VC
Experiment	0.0006	0.0004
Breed	0.003	0.001
Residual	0.006	0.003
PCV _[Experiment]	–	33%
PCV _[Breed]	–	66%
PCV _[Residual]	–	50%
$R^2_{LMM(m)}$		43.59%
$R^2_{LMM(c)}$		61.52%
DIC	-136.62	-172.24

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.8 Summary of the statistical results from the early-pregnancy subgroup analysis using the natural logarithm of the response ratio (lnRR).

Description	Early-pregnancy subgroup models		
	Meta-analysis	Meta-regression #1	Meta-regression #2
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	-0.001 [-0.03 – 0.03]	-0.00002 [-0.04 – 0.03]	-0.0009 [-0.03 – 0.03]
Total days	–	-0.02 [-0.06 – 0.009]	–
Outcome day	–	–	-0.03 [-0.07 – -0.0004]
Random effects	VC	VC	VC
Experiment	0.0008	0.0008	0.0006
Residual	0.001	0.001	0.001
PCV _[Experiment]	–	0%	25%
PCV _[Residual]	–	0%	0%
$R^2_{LMM(m)}$	–	17.53%	36.63%
$R^2_{LMM(c)}$	–	49.82%	58.94%
DIC	-68.69	-68.77	-71.08

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.9 Summary of the statistical results from the mid-pregnancy subgroup analysis using the natural logarithm of the response ratio (lnRR).

Description	Mid-pregnancy subgroup models		
	Meta-analysis	Meta-regression #1	Meta-regression #2
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	0.02 [-0.02 – 0.06]	0.03 [-0.009 – 0.07]	0.03 [-0.02 – 0.07]
End day of manipulation	–	-0.04 [-0.08 – -0.002]	–
Outcome day	–	–	-0.03 [-0.08 – 0.007]
Random effects	VC	VC	VC
Experiment	0.002	0.001	0.002
Residual	0.002	0.002	0.002
PCV _[Experiment]	–	50%	0%
PCV _[Residual]	–	0%	0%
R ² _{LMM(m)}	–	39.78%	24.44%
R ² _{LMM(c)}	–	63.12%	55.44%
DIC	-64.65	-68.33	-66.82

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.10 Summary of the statistical results from the late-pregnancy subgroup analysis using the natural logarithm of the response ratio (lnRR).

Description	Late-pregnancy models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.10 [-0.14 – -0.06]	-0.10 [-0.15 – -0.07]
Total days		-0.03 [-0.07 – 0.01]
Random effects	VC	VC
Experiment	0.002	0.002
Residual	0.004	0.004
PCV _[Experiment]	–	0%
PCV _[Residual]	–	0%
R ² _{LMM(m)}		10.22%
R ² _{LMM(c)}		35.22%
DIC	-77.66	-76.13

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Table S2.11 Summary of the statistical results of meta-analytic and meta-regression models in the overnutrition datasets using the natural logarithm of the response ratio (lnRR).

Description	Overnutrition models	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	0.020 [-0.02 – 0.06]	-
Singletons (intercept)	-	0.07 [0.003 – 0.14]
Twins (intercept)	-	-0.003 [-0.05 – 0.04]
Total days (slope)	-	-0.03 [-0.07 – 0.004]
Random effects	VC	VC
Experiment	0.003	0.002
Residual	0.002	0.002
PCV _[Experiment]	-	33%
PCV _[Residual]	-	0%
$R^2_{LMM(m)}$		35.97%
$R^2_{LMM(e)}$		65.56%
DIC	-72.18	-70.15

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion.

95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (in bold).

Chapter 3: Meta-analysis of the role of pregnancy nutrition in adult multiparous ewes in determining changes in lamb birth weight

3.1 Abstract

There is a large variation in lamb birth weight responses to changes in the ewe nutrition during pregnancy. Much of this variation (or heterogeneity) has been attributed to experimental factors inherent to each experiment. However, to date, the contribution of these experimental factors to this variation has not been quantified. This meta-analysis was set to determine this variation in lamb birth weight responses across 70 nutritional studies in adult sheep. Effect sizes for individual studies were estimated using the unbiased estimator Hedges' g , and thus, positive and negative values indicate heavier and lighter treatment lambs vs. controls, respectively. Heterogeneity varied between early-, mid- and late-pregnancy undernutrition studies ($I^2_{\text{total [early-pregnancy]}} = 19.90\%$, $I^2_{\text{total [mid-pregnancy]}} = 52.10\%$, $I^2_{\text{total [late-pregnancy]}} = 68.70\%$). The pooled effects for early- (0.01, HPD = -0.26 – 0.28) and mid-pregnancy undernutrition (-0.07, HPD = -0.27 – 0.16) suggest that if farmers anticipate a potential feed shortage, ewes can be allowed to lose weight if nutrition is resumed to adequate levels later in pregnancy. On the contrary, late-pregnancy undernutrition was associated with a significant decrease in lamb birth weight (-0.75, HPD = -0.92 – -0.60). Thus, management practices should focus on minimizing potential losses by prioritizing the available feed to ewes in poor body condition and those bearing multiples. Increasing lamb birth weight may be possible by feeding ewes above their pregnancy maintenance requirement (0.23, HPD = 0.002 – 0.48), though literature is limited and further research is needed to extend and support the current evidence.

Key words: meta-analysis, birth weight, sheep, maternal nutrition

3.2 Introduction

In New Zealand, 20 years of improvements in animal genetics, health and farm management have led to significant on-farm productivity gains (Mackay, 2012). One major gain observed in the New Zealand sheep flock has been the increased ewe fecundity, which has led to an increase in lambing percentages across the regions (Morris and Kenyon, 2014). However, a negative relationship still exists between the number of lambs born and their survival (Stafford, 2013). Whilst there have been significant efforts to improve lamb survival, lamb mortality remains a key economic and welfare issue for sheep producers (Morris and Kenyon, 2014). Not just limited to New Zealand, it is estimated that worldwide lamb mortality rates range between 9% and 30% (Binns et al. 2002; Dwyer, 2008; Mousa-Balable, 2010), with around 70% of lamb deaths occurring within 24 - 48 hours after birth (Hall et al. 1995; Mellor and Stafford, 2004).

Birth weight is considered the single greatest predictor for lamb mortality (Fogarty et al. 2000). Indeed, the incidence of morbidity and mortality during the neonatal period is known to be high at the birth weight extremes (Alexander, 1974; Everitt-Hincks and Dodds, 2007; Oldham et al. 2011). Low birth weight lambs are particularly vulnerable to starvation and hypothermia (Nowark and Poindron, 2006), whereas heavy lambs are more likely to die during difficult deliveries (Dwyer, 2008), often referred to as dystocia.

The nutrition of the pregnant ewe has been shown to influence lamb birth weight in both biomedical and agricultural studies. A number of traditional and systematic reviews (Harding 2001; Rhind et al. 2001, 2003; Greenwood and Bell 2003; Rhind, 2004; McMillen and Robinson 2005; Bell 2006; Wu et al. 2006; Greenwood and Thompson,

2007; Caton and Hess, 2010; Kenyon and Blair, 2014; Rooke et al. 2015) have acknowledged that late pregnancy maternal undernutrition can result in lambs that are lighter at birth compared to controls. By contrast, these reviews indicate that early- and mid-pregnancy undernutrition (Greenwood and Bell, 2003; Gardner et al. 2007; Bell and Greenwood, 2016) and overnutrition of mature ewes (Kenyon and Blair, 2014; Bell and Greenwood, 2016) have only a small impact on lamb birth weight. However, results across the reviewed studies have been somewhat variable in magnitude (see reviews by Greenwood and Bell, 2003; Kenyon and Blair, 2014; Bell and Greenwood, 2016). This uncertainty and inconsistency in estimated effects has been largely attributed to factors related to feeding regimens, experimental designs and disparity between diets across studies. To date, however, the contribution of these factors on the variability in study results has not yet been quantified.

In the previous chapter, quantitative synthesis in the form of meta-analysis was used to quantify the effect of maternal nutrition during pregnancy on late-gestation fetal weight. It was estimated that failing to meet the ewe's nutritional requirements in late-pregnancy is likely to decrease fetal weight close to term by up to 20%. On the contrary, early- and mid-pregnancy undernutrition or relative overnutrition of adult ewes had no significant effects on late-gestation fetal weight. In the present study, a similar meta-analytic approach was undertaken to answer three main questions: firstly, given that individual experiments are highly variable, what can this distribution of findings tell about the optimum nutrition of the pregnant ewe? Secondly, what experimental variables are driving the variability in results? Thirdly, what is the biological relevance of the combined evidence across studies from an agricultural perspective? The hypotheses tested were that undernutrition during

late-pregnancy or long-term undernutrition that extended into late-pregnancy would result in lighter lambs at birth when compared to lambs from control dams. In contrast, it was hypothesised that early- and mid-pregnancy undernutrition would only have a small negative impact on lamb birth. Finally, it was further hypothesised that maternal overnutrition would result in heavier lambs at birth compare to their control counterparts.

3.3 Materials and methods

Currently, many reporting guidelines exist for the publication of systematic reviews and meta-analysis in the Health and Social Sciences. The main purpose of these guidelines is to improve the clarity, quality and transparency of these reports by promoting the description of a minimum set of elements, which are key for a critical appraisal of published literature. No such guidelines currently exist for publication of meta-analyses in the Animal Sciences. For this reason, the present study has adopted, where possible, the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” statement (PRISMA; Moher et al. 2009). The PRISMA statement consists of a 27-item checklist describing the main information that needs to be specified in a meta-analysis. In addition, a four-phase flow diagram is available, that allows visual assessment of the processes undertaken from literature search to final inclusion/exclusion decisions.

3.3.1 Search strategy and selection criteria

The initial literature search was conducted in the online databases PubMed, SCOPUS and Web of Knowledge (WoK) to identify studies published up to 22 July 2014. The pre-specified search string included the terms sheep, birth weight, maternal nutrition, pregnancy, IUGR and their variants using Boolean operators (see 3.8.1 Supplementary

methodology). This initial search was carried out without publication date and language restrictions. In addition, references of the previous chapter were scrutinized for potential studies not found in the initial database search. All these retrieved records were screened to find potentially relevant studies and key reviews. These relevant records were further inspected for papers cited (i.e. forwards search) and papers citing (i.e. backward search) in order to find papers that were potentially missed by the initial search.

Experimental articles were assessed for eligibility based on full text, supplementary materials and information obtained directly from the authors. Potentially relevant studies were selected on the basis of the following criteria: (1) studies had to be undertaken in adult, multiparous sheep; (2) the breed of sheep used in each experiment had to be stated in the text; (3) have information detailing nutritional manipulations during pregnancy (periconceptual and flushing periods included); (4) provide birth weight data for naturally-born lambs for both control and treatment groups; (5) birth weight statistics had to be reported for each individual birth type, (6) had sufficient information to calculate an effect size between a control and a nutritionally manipulated group. The required information to calculate an effect size included: the number of lambs in each treatment, the mean birth weight for each treatment and their corresponding measurement of dispersion, and whether the study was undertaken in singletons or twins.

Studies failing to comply with these minimum requirements were excluded. Additionally, review papers, cohort studies of previously reported experiments, studies in triplet-bearing ewes and adolescent (7 to 10 months of age at breeding) or nulliparous (first lambing regardless of age) sheep were also excluded. Lastly, in studies where mid-pregnancy

shearing and nutrition during pregnancy were undertaken simultaneously, only data of the unshorn control and nutritionally manipulated groups were included.

3.3.2 Data extraction

The main data for this study were extracted from information presented in tables, figures and text. GraphClick (Arizona-Software, Los Angeles, CA, USA; Boyle et al. 2013) was used to extract relevant information presented as figures. If essential information (e.g. sample size, birth weight, litter size) was missing from the articles, authors were contacted by e-mail only if the article was published after the year 2000. The contacted authors were provided with a brief description of the meta-analysis, complete article citation, the specific information needed and a request for unpublished data (see Acknowledgements for details). If adequate clarification or data could not be provided the study was excluded.

3.3.3 Data coding and datasets

Extracted data from the selected studies was coded to generate an initial dataset. The extracted data included: first author name, year of publication and journal, study ID and experiment ID (sometimes there were more than one independent experiment presented in a single study), mean lamb birth weights, variance and sample sizes for the control and experimental groups and the type of nutritional manipulations (i.e. undernutrition or overnutrition). When lamb birth weight data were presented for males and female independently within the same study ($n = 9$), these data were pooled. An additional identifier variable was coded to account for potential correlated structures within the data (e.g. control group ID), since in many studies multiple treatment groups were compared to one common control. The following relevant information was also collected to explain

potential heterogeneity and bias in the data: (1) the type of housing used for the experiment (e.g. indoors or outdoors); (2) litter size (i.e. coded as a binary variable with 1 being singletons and -1 for twins), (3) dam breed, (4) total number of days of the nutritional manipulation (total days), (5) day of pregnancy when the nutritional manipulation started (start day) and (6) day of pregnancy when the nutritional manipulation finished (end day). This latter predictor variable was coded as a continuous and as a categorical variable. The categorical transformation of end day had three levels that corresponded to nutritional manipulations ending within each stage of pregnancy: Early-pregnancy included all studies with nutritional manipulation that finished before day 35 of pregnancy. Mid-pregnancy comprised of all studies where the nutritional manipulations started after day 35 of pregnancy but that finished before day 105 of pregnancy. Late-pregnancy, included all remaining studies whose nutritional manipulation finished after day 105. Lastly, the level of feeding of the control group was coded as either pregnancy maintenance (PM) or above pregnancy maintenance (WF). Where authors stated the level of feeding of the control group as PM or above PM, this was adopted. If the level of feeding of the control group was not available, it was estimated from the ewe live weight data provided in the manuscript.

In the present study, the term “pregnancy maintenance requirements” is defined as the amount of energy required to maintain ewe net live weight throughout pregnancy, whilst allowing for adequate growth of the fetus (or fetuses) at each individual stage of pregnancy. Any nutritional manipulation below and above this threshold is referred to as undernutrition or overnutrition, respectively. Based on the different experimental set-ups found in the literature, the initial dataset was split in two main datasets for analysis:

1. Undernutrition (UN) dataset: The extracted data involved the comparison between experimental ewes fed below PM requirements and a control-fed group. The selected undernutrition studies often differed in the type of control group used for each specific experiment (PM or WF). Some studies were conducted so they had a PM-fed group (used as control), an underfed and an overfed group. In these cases, both, the PM-fed and overfed groups were used as “controls” for the undernutrition group.
2. Overnutrition (ON) dataset: This dataset only compared a control group of ewes that were fed to meet their PM requirements against an experimental group fed above their PM requirements (i.e. overfed group).

3.3.4 Statistical analysis

To quantify the birth weight responses to maternal nutrition, Hedges’ g (Hedges, 1981) was used as the effect size metric for this study. Hedges’ g in the present study represents the standardised mean difference in birth weight between the experimental group and the control group in terms of the pooled standard deviation, with a correction for small sample sizes (Hedges, 1981; Nakagawa and Cuthill, 2007). A positive value of g can therefore be interpreted as an increase in lamb birth weight in the experimental group relative to the controls. A negative value of g can be interpreted as a decrease in lamb birth weight in the treatment group relative to the controls. Treatment effects are discussed based on Cohen (1988) interpretative guidelines, where the magnitude of an effect can be classified as small ($g = 0.2$), moderate ($g = 0.5$) or large ($g = 0.8$).

3.3.4.1 Meta-analysis

All statistical analyses were performed using *R* v.3.0.2 (R Development Core Team, 2013). The two main datasets were analysed independently using Bayesian multilevel mixed-effects meta-analysis as implemented in the *MCMCglmm* package (Hadfield, 2010; Hadfield and Nakagawa, 2010). Two main models were used to summarize the results across studies and to explore potential sources of variation across studies (i.e. traditional meta-analysis and meta-regression, respectively):

Model I: Traditional random-effects meta-analysis was used to estimate the mean effect across studies. For the undernutrition dataset, this intercept-only model included the random effects of dam breed and experiment identity. Only experiment identity was used for the overnutrition dataset. These meta-analytic models can be written as (following notation by Gelman and Hill, 2007; Nakagawa and Santos, 2012):

$$\begin{aligned}g_i &= \alpha + s_{j[i]} + b_{k[i]} + e_i + m_i, \\ \mathbf{s} &\sim N(\mathbf{0}, \sigma_{exp}^2 \mathbf{I}), \\ \mathbf{b} &\sim N(\mathbf{0}, \sigma_{breed}^2 \mathbf{I}), \\ \mathbf{e} &\sim N(\mathbf{0}, \sigma_e^2 \mathbf{I}), \\ \mathbf{m} &\sim N(\mathbf{0}, \mathbf{M}),\end{aligned}$$

where g_i is the observed effect-size, α is the overall intercept or meta-analytic mean, $s_{j[i]}$ denotes the experiment-specific effect for the j th experiment ($j = 1, \dots, N_{experiment}$) applied to the i th effect size ($i = 1, \dots, N_{effect-size}$; $N_{effect-size}$ is the number of effect-sizes), \mathbf{s} is a 1 by

$N_{experiment}$ vector, which is normally distributed around 0 with the between-experiment variance of σ_{exp}^2 (which was unknown but estimated from the data), $\mathbf{0}$ is a 1 by $N_{experiment}$ vector of 0 and \mathbf{I} is the $N_{experiment}$ by $N_{experiment}$ identity matrix; $b_{k[i]}$ (only used in the undernutrition meta-analysis) is the breed-specific effect for the k th breed ($k = 1, \dots, N_{breed}$; ; N_{breed} is the number of breeds) applied to the i th effect size estimate, and \mathbf{b} is a 1 by vector of b_j , which is normally distributed around 0 with breed-specific variance of σ_{breed}^2 (which was unknown but estimated from the data); e_i is the within-experiment effect for the i th effect-size, and \mathbf{e} is a 1 by $N_{experiment}$ vector of e_j , which is normally distributed around 0 with the within-experiment variance of σ_e^2 (which was unknown but estimated from the data). Lastly, m_i is the sampling error effect for the i th effect-size, \mathbf{m} is a 1 by $N_{experiment}$ vector of m_j , which is normally distributed around 0 with the typical sampling error variance of σ_m^2 (see details in “heterogeneity” section as to how this was estimated), and \mathbf{M} is a $N_{experiment}$ by $N_{experiment}$ matrix, with its diagonal elements being σ_m^2 , which is assumed to be known.

Model II: Meta-regressions were constructed as mixed-models which incorporated the following potential predictor variables: i) level of nutrition of the control group (PM vs. WF; undernutrition dataset only), ii) litter size (coded as a binary variable with 1 being singletons and -1 for twins), iii) total days iv) start day, v) end day, vi) year of publication and vii) housing type. These meta-regression models were given by:

$$g_i = \theta_i + s_{j[i]} + b_{k[i]} + e_i + m_i,$$

$$\theta_i = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} \dots \beta_n x_{nj},$$

where β_0 is the intercept, $\beta_{1\dots n}$ are regression coefficients and represent the change in effect-size for unit increase in x , with $x_{1\dots n}$ being the values for the predictor variables (where $j = 1\dots N_{\text{experiment}}$). All other symbols are the same as above. All continuous predictors were z -scaled (that is, they had a mean of 0 and standard deviation of 1). Their regression coefficients can therefore be interpreted as the amount of change in effect size when the predictor value changes by one standard deviation.

Three independent Markov Chain Monte Carlo (MCMC) chains were run for each model. Each chain was run for 130,000,000 iterations with a thinning of 1,000,000 after 30,000,000 iterations of burn-in. Random effects for all models were run with the expanded parameter inverse-Wishart prior (the parameter settings in *MCMCglmm*: $V = 1$, $nu = 0.002$, $alpha.mu = 0$, $alpha.V = 1000$), whilst we used the default prior (a diffused non-informative prior) for fixed effects. Model convergence and mixing were assessed using the Gelman-Rubin statistic (Gelman and Rubin, 1992) and autocorrelation within chains, respectively. Chain selection was performed by choosing the chain with the lowest deviance information criterion (DIC, Spiegelhalter et al. 2002). Interdependence of effect sizes arising from multiple treatment groups being compared to a common control groups was statistically controlled for by estimating variance and covariance values adjusted for the presence of a common control group using the methods reported by Gleser and Olkin (2009). The calculated variance-covariance matrix of the shared identities (identified through the control ID variable) was incorporated into the statistical models.

For each model, information about the posterior mode, mean, standard deviation and 95% highest posterior density (HPD) intervals was collected for meta-analytic model intercepts

and predictor slopes. In the present study, the posterior mean is reported as the point estimate of the meta-analysis. The estimates were considered statistically different from zero only if the 95% HPD intervals did not include zero.

3.3.4.2 *Heterogeneity*

The assessment of the consistency of results across studies is an essential part of meta-analysis (Higgins et al. 2003). In addressing the effect of maternal pregnancy nutrition on birth weight, studies differ in various aspect of study design. As a result, outcomes differ across studies. In meta-analysis, such dispersion or variability in study outcomes is commonly known as heterogeneity.

The extent of heterogeneity within each dataset was estimated by an extended version of the I^2 index proposed by Higgins and Thompson (2002) in which the percentage of variance at each random effect is considered in relation to the sum of all variance components (see Nakagawa and Santos, 2012; cf. Cheung, 2014) and was calculated as:

$$I^2 = \frac{\sigma_t^2 - \sigma_m^2}{\sigma_t^2} \times 100$$

where σ_t^2 is the sum of all variance components and σ_m^2 is the typical sampling error variance, which can be defined as:

$$\sigma_m^2 = \frac{\sum_{i=1}^k w_i (k-1)}{(\sum_{i=1}^k w)^2 - \sum_{i=1}^k w_i^2}$$

where w_i is the inverse of the i th measurement error variance associated with the i th g estimate ($i = 1, \dots, k$).

In the UN dataset, σ_t^2 was defined by:

$$\sigma_t^2 = \sigma_{exp}^2 + \sigma_{breed}^2 + \sigma_e^2 + \sigma_m^2$$

whereas in the ON dataset and undernutrition subgroups, it was defined by:

$$\sigma_t^2 = \sigma_{exp}^2 + \sigma_e^2 + \sigma_m^2$$

where σ_{exp}^2 is the experiment-level variance, σ_{breed}^2 is the dam breed-level variance, σ_e^2 is the residual variance (to be explained by our predictors). Therefore, the proportion of variance at each random effect in relation to the total sum of variance components is $\sigma_{exp}^2/\sigma_t^2$ and is $\sigma_{breed}^2/\sigma_t^2$, respectively.

3.3.4.3 R^2 estimation for meta-regression models

To determine the contribution of fixed and random effects to explaining variation in the responses across studies in the meta-regression models, two R^2 statistics were calculated as suggested by Nakagawa and Schielzeth (2013). The marginal R^2 measures the variance explained by the fixed effects as a proportion of the sum of all variance components and was defined as:

$$R_{LMM(m)}^2 = \frac{\sigma_f^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

where σ_f^2 is the variance attributable to the fixed effects, σ_l^2 is the variance component of the l th random factor, σ_e^2 is the residual variance. Note that σ_m^2 is not part of the formula, as it is considered to be explained already. In addition, the conditional R^2 determines the

variance explained by fixed and random factors and was calculated by integrating into the numerator the variance explained by the random factors:

$$R_{LMM(c)}^2 = \frac{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

3.3.4.4 Publication bias

Publication bias is the term used to describe the impact of studies with statistically significant results being more likely to be published than those reporting non-statistically significant results (Rothstein et al. 2005). In the present study, examination for potential publication bias was performed by visual inspection of funnel plots for the presence of data distribution asymmetry (Rothstein et al. 2005), and by formal testing of funnel plot asymmetry using Egger's regression approach (Egger et al. 1997). Given the non-independent nature of the collected data, the Egger's regression test was applied to data points consisting of the residual and sampling errors from the meta-regression models as suggested by Nakagawa and Santos (2012).

3.3.4.5 Sensitivity analysis

Low sample size and therefore, low statistical power may lead to exaggerated estimates of the magnitude of an effect and can result in low reproducibility across experiments (Button et al, 2013). To test the robustness of the estimates in the main analyses, studies with sample sizes of five lambs or less (in either the control or treatments group) were removed from the main dataset before re-running all the statistical models. In addition, influential studies were removed from the dataset to test if the exclusion of these studies would lead to

considerable changes in the conclusions of this meta-analysis. Due to the availability of data, this sensitivity analysis was only performed in the undernutrition dataset.

In this study, the trim-and-fill method (Duval and Tweedy, 2000) was used to adjust the estimates for potential publication bias. The trim-and-fill method assesses asymmetry in the funnel plot and imputes the number of suspected missing studies. The adjusted result can be used as sensitivity analysis to indicate the extent to which publication bias may have affected the results from this study.

3.4 Results

3.4.1 Study retrieval and selection strategy

The course of the systematic review in the present study is illustrated in the four-phase flow diagram following the PRISMA statement (Figure 13). The electronic search of PubMed, SCOPUS and WoK databases provided a total of 4872 potentially relevant citations after adjusting for duplicates. An additional 22 studies were identified by examining 108 key reviews found in the original search. After title, abstract and occasional full-text scan, 4388 studies were excluded because they clearly did not meet the criteria for inclusion or were irrelevant to our research question. The remaining 506 studies were examined in more detail as they were identified as reporting relevant information related to the effect of maternal nutrition during pregnancy and lamb birth weight. Of these, 435 studies did not meet the inclusion criteria and were excluded from the study (see Figure 13 for details of exclusion; also 3.8.2 Supplementary references – list of excluded studies). Authors were contacted for additional information related to 16 studies. Authors from 9 studies provided written clarification about their experiments and 6 authors provided their original data. No

unpublished or other relevant data were obtained. Finally, 70 suitable studies were identified representing two major experimental set-ups: relative undernutrition ($n = 61$) and overnutrition ($n = 15$). Some studies reported on experiments undertaken in both experimental set-ups (under and overnutrition).

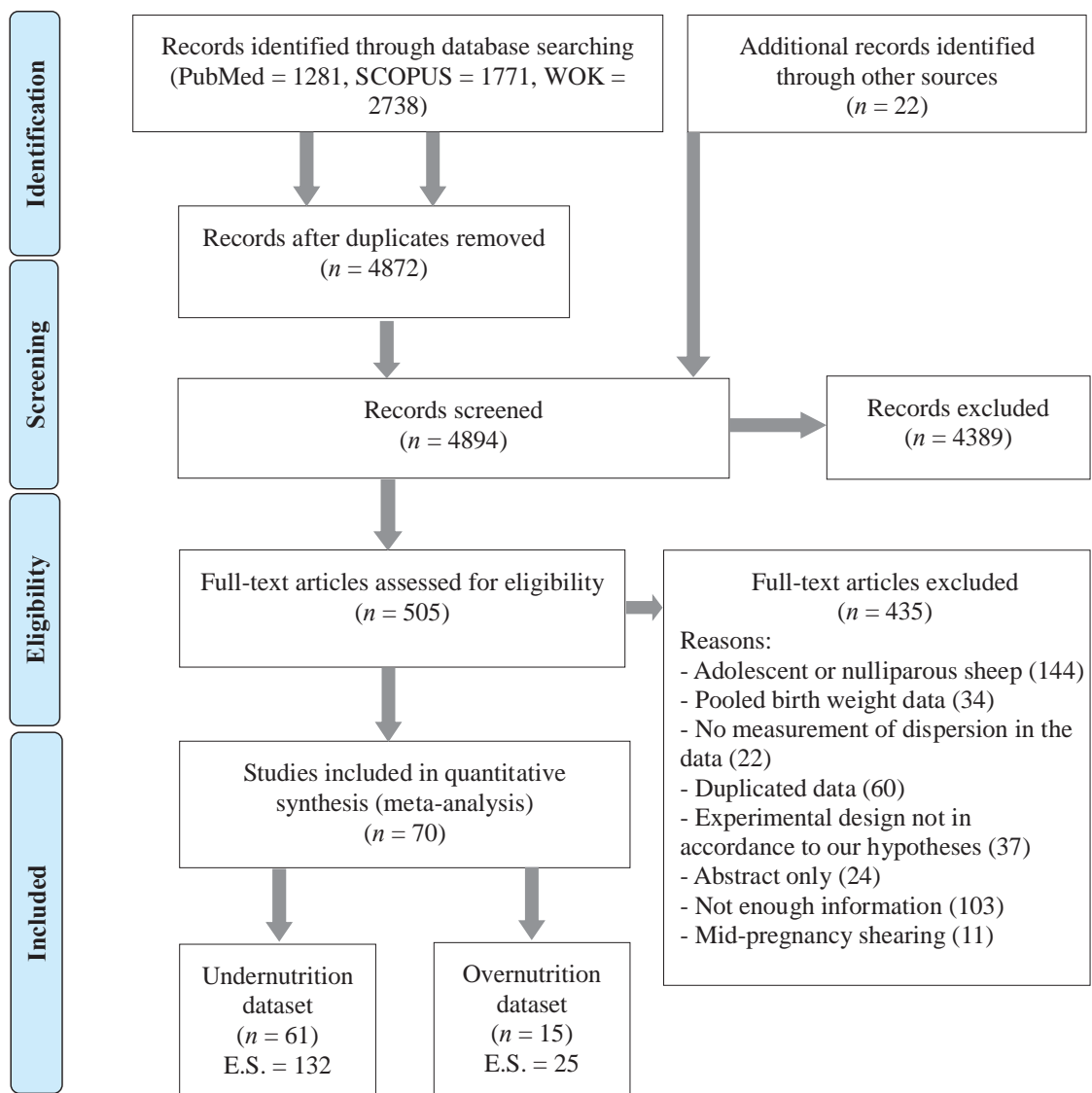


Figure 13. Four-phase flow diagram following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. The number of studies in each category is shown in parenthesis. The number of effect-sizes (E.S.) are given for each dataset.

3.4.2 Study characteristics and meta-analysis

3.4.2.1 *Undernutrition*

The undernutrition dataset consisted of 61 primary studies involving 68 different experiments. A total of 132 observations were extracted from these primary studies and were used for meta-analysis. Observations used for analysis had been conducted across a time span of 66 years, dispersed across years as follows: 9% before the 1970's, 32% between 1970 and 1990, 7.5% between 1991 and 2000, 23% between 2001 and 2007 and 28% between 2008 and 2014. Although no author or set of authors dominated in contributions to the dataset (the most being 13% for a single researcher; Holst et al. 1986), almost 80% of observations originated from three locations: Australia (28%), New Zealand (19%) and the United Kingdom (33%). The remainder of the records were distributed among 11 countries.

Over all the experiments analysed, maternal undernutrition during pregnancy resulted in lambs that were half a standard deviation lighter than their control counterparts (Supplementary Table S3.1: Meta-analytic model). This initial analysis, however, indicated a large degree of variation across studies ($I^2_{\text{total}} = 76.30\%$, $I^2_{\text{between-experiments}} = 17.10\%$, $I^2_{\text{between-breeds}} = 23.90\%$ and $I^2_{\text{residual}} = 35.30\%$), thereby, further examination of this variability was warranted. There were considerable differences in the overall effect of undernutrition depending on the “timing of nutritional manipulations” (that is, whether nutritional manipulations finished within early, mid- or late-pregnancy; Supplementary Table S3.1: Meta-regression model; Figure 14). Overall, undernutrition in early- and mid-pregnancy was found to have no significant effect on lamb birth weight ($\beta_{[\text{Early-pregnancy}]} =$

0.04, 95% HPD = -0.22 to 0.28, $\beta_{[\text{Mid-pregnancy}]} = -0.15$, 95% HPD = -0.35 to 0.05), whereas, maternal undernutrition during late pregnancy and long-term undernutrition extending into late-pregnancy resulted in a significant decrease in lamb birth weight ($\beta_{[\text{Late-pregnancy}]} = -0.72$, 95% HPD = -0.86 to -0.55). This single-predictor meta-regression model was able to explain over 70% of the variation in the data and reduced both the experiment and residual level variances by 65% and 48%, respectively. The decrease in 54% in the variance attributable to breed differences suggested that breed and the timing of undernutrition were confounded by experimental design (i.e. some breeds being used in only one stage of pregnancy) and this was not investigated further.

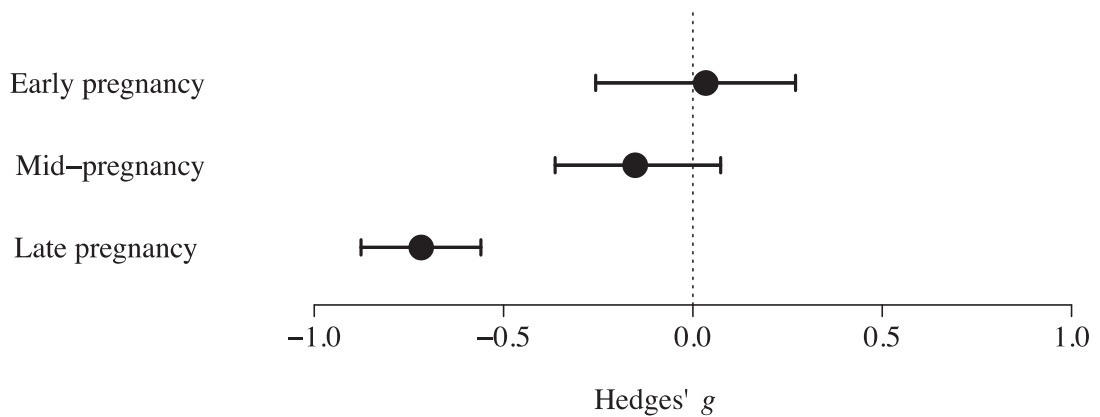


Figure 14. Forest plot of estimates from the meta-regression of the undernutrition dataset. Posterior means for each period of pregnancy (intercepts) are represented by circles. Horizontal lines represent 95% highest posterior density (HDP) intervals. Zero effect is shown as a vertical dashed line. Statistically significant effects are considered those whose 95% HDP do not cross zero.

An additional model is presented in Supplementary Table S3.1 to demonstrate that there were no significant effects of litter size (representing the differences in magnitude between studies in singletons and twins) and length of nutritional manipulations across the selected

studies. However, a significant effect for publication year was found, whereby articles published earlier than 1994 observed more severe effects than those published in later years ($\beta_{[\text{Publication year}]} = 0.21$, 95% HPD = 0.07 to 0.34). The inclusion of these predictors did not explain the variation between studies beyond that already explained by the timing of undernutrition. On the basis of these results, subgroup analyses were performed to uncover potential sources of variation within studies undertaken at each stage of pregnancy.

A summary of the main characteristics of the studies included in the subgroup analyses is presented in Supplementary Table S3.2. Results from these subgroup analyses confirmed the marked differences in birth weight responses to undernutrition at the different stages of pregnancy but also revealed varying levels of heterogeneity in each subgroup ($I^2_{\text{total [early-pregnancy]}} = 19.90\%$, $I^2_{\text{total [mid-pregnancy]}} = 52.10\%$, $I^2_{\text{total [late-pregnancy]}} = 68.70\%$).

Studies in the early-pregnancy subgroup (Table 4) represented two main experimental setups: early-pregnancy undernutrition (i.e. UN starting at mating) and periconceptual undernutrition (i.e. UN starting long before mating). The meta-analysis indicated that there is no significant overall effect of undernutrition on lamb birth weight ($\beta_{[\text{meta-analytic mean}]} = 0.01$, 95% HPD = -0.26 to 0.28). The limited number of studies prevented further exploration of potential predictors. Although, from Table 4 and Figure 15 it is clear that undernutrition starting at or close to mating and lasting between 30 to 45 days resulted in minor and non-significant effects (that is, the significance found in each study) on lamb birth weight irrespective of litter size. With the exception of one study (Oliver et al. 2005), periconceptual undernutrition starting 60 days before mating appeared to have differential effects on singletons (marked in red) and twins (marked in grey).

Table 4. Summary of papers used for meta-analysis in the early-pregnancy subgroup. Liveweight (LW) change refers to the difference in ewe live weight between the commencement of the nutritional treatment and that at the end of the nutritional treatment. The energetic level of undernutrition (relative to maintenance) is shown when and as stated by the authors.

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Chadio, 2007	Greece	50% - ↓~0.6 kg	0 - 30	T	Indoors	Male + Female = -100
Cleal, 2007	England	50% - ↑~0.8 kg	0 - 30	S and T	Indoors	Male + Female (single) = +200
Gardner, 2005	England	50% - ↑~0.6 kg	0 - 30	S	Indoors	Male + Female (twin) = 0
Khan, 2005	England	50%	0 - 31	S	Indoors	Male = +400
Parr, 1986	Australia	50% - ↓~5 kg	1 - 35	S	Indoors	Average Male + Females = +40
Hernandez, 2009	New Zealand	NE	-2 - 30	S	Indoors	Male + Female = +650
Jaquierey, 2012	New Zealand	NE	-2 - 30	S	Indoors	Male + Female = +150
Debus, 2012	France	50% - ↓~5.2 kg	-15 - 30	S and T	Indoors	Male + Female (single) = +40 Male + Female (twin) = +100
Smith, 2010	Ireland	70% - ↓~2.6 kg	-28 - 7	S and T	Indoors	Male + Female (single) = +50 Male + Female (twin) = 0
Hernandez, 2009	New Zealand	NE	-61 - 30	S and T	Indoors	Male + Female (single) = +700 Male + Female (twin) = -250
Jaquierey, 2011	New Zealand	NE	-61 - 30	S and T	Indoors	Male + Female (single) = +700 Male + Female (twin) = -200
Jaquierey, 2012	New Zealand	NE	-61 - 30	S	Indoors	Male + Female = +1100
Oliver, 2005	New Zealand	↓~8 kg	-61 - 30	S	Indoors	Male + Female = -850

† NE = Non-estimable from the provided information.

§ days of pregnancy, where 0 (conception) and 150 (~term).

* S = Singletons, T = Twin

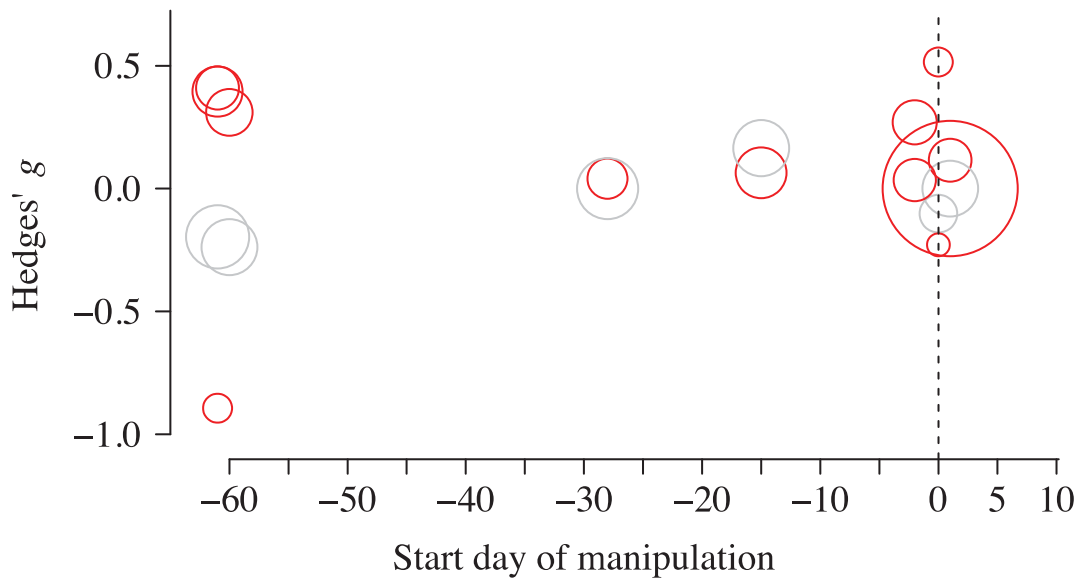


Figure 15. Bubble plot depicting the differences in birth weight responses to maternal undernutrition starting before or at mating (day 0, shown in dashed line). Bubbles represent the effect sizes for experiments undertaken in singleton- (red) and twin-bearing ewes (grey). Differences in bubble circumference demonstrate differences in the precision (1/standard error) between studies.

The mid-pregnancy subgroup corresponded to studies examining the effect of early-to-mid and mid-pregnancy undernutrition (Figure 16, Table 5). Overall, undernutrition had no significant effect on lamb birth weight ($\beta_{[\text{meta-analytic mean}]} = -0.07$, 95% HPD = -0.27 to 0.16). Experimental replication (the number of experiments available within a particular timeframe) was low in this data subgroup (see Table 5), which resulted in a moderate variation in birth weight responses (on both directions) to the different nutritional manipulation ($I^2_{\text{total}} = 52.10\%$). Indeed, 85% of this variation in results was attributed to differences between experiments ($I^2_{\text{between-experiment}} = 44.40\%$) with little residual variance ($I^2_{\text{residual}} = 7.70\%$). No individual predictor helped to further explain the residual heterogeneity in this subgroup, although it was noted that the variance at the experiment

level was reduced by 20% when “control group type” (PM vs. WF) was used as a fixed effect in the meta-regression (Supplementary Table S3.3).

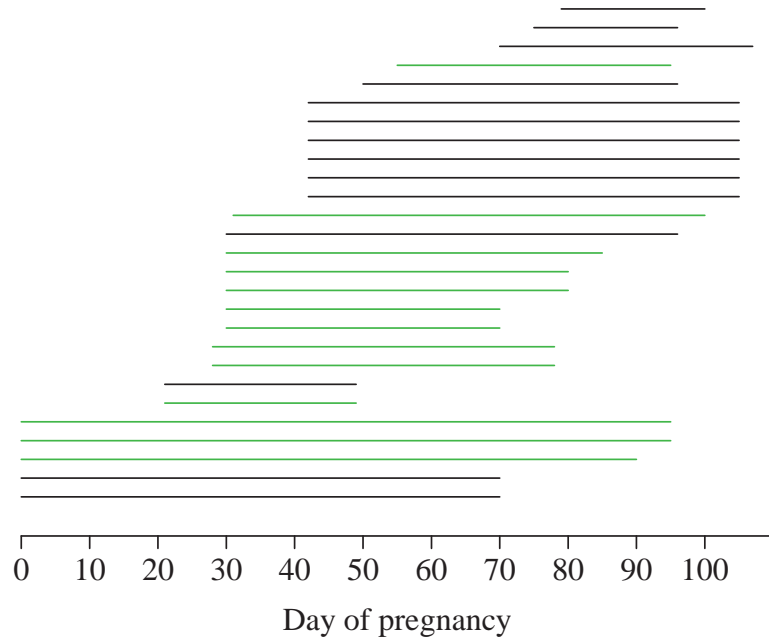


Figure 16. Line plot representing the nutritional manipulations for each observation in the mid-pregnancy subgroup. Lines of different colour represent studies using a control groups fed to meet their pregnancy maintenance requirements (PM; in green) or a control groups fed above PM requirements (in grey), respectively.

Table 5. Summary of papers used for meta-analysis in the mid-pregnancy subgroup. Liveweight (LW) change refers to the difference in ewe live weight between the commencement of the nutritional treatment and that at the end of the nutritional treatment. The energetic level of undernutrition (relative to maintenance) is shown as stated by the authors.

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Krausgrill, 1999	Australia	Exp 1 = ↓~8 kg Exp 2 = ↓~15 kg	0 – 70	S	Indoors	Experiment 1 - Male + Female = -500 Experiment 2 - Male + Female = +400
Everitt, 1967	Australia	↓~8 kg	0 – 90	S	Outdoors	Male + Female = -258
Hyatt, 2007a	England	50%	0 – 95	S	Indoors	Male = -430
Rae, 2002	Scotland	50%	0 – 95	S	Indoors	Male + Female = -105
Kenyon, 2011	New Zealand	↓~5.2 kg	21 – 49	T	Outdoors	PM control - Male + Female = -140 AL control - Male + Female = 0
Burt, 2007	United States	50% - ↓~6.2 kg	28 – 78	S	Indoors	UW ewes - Female = +200 Baggs ewes - Female = -100
Daniel, 2007	England	50%	30 – 70	T	Indoors	Male + Female = -40
Fahey, 2005	England	50%	30 – 70	T	Indoors	Male + Female = +40
Sebert, 2009	England	50%	30 – 80	T	Indoors	Male + Female = -100
Sen, 2013	Turkey	50% - ↓~4 kg	30 – 80	S	Indoors	Male + Female = -470
Daniel, 2007	England	50%	30 – 85	T	Indoors	Male + Female = +85
McCrabb, 1992	Australia	↓~4.3 kg	30 – 96	S	Outdoors	Male + Female = -270
Chadio, 2007	Greece	50% - ↓~4.5 kg	31 – 100	T	Indoors	Male + Female = -350

Table 5. continued...

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Holst, 1986	Australia	Exp 1 = ↓~9 kg	42 – 105	S and T	Outdoors	Male + Female (single, Experiment 1) = -100
		Exp 2 = ↓~6.5 kg				Male + Female (single, Experiment 2) = +430
		Exp 3 = ↓~5.8 kg				Male + Female (single, Experiment 3) = +300
McCrabb, 1992	Australia	↓~3.1 kg	50 – 96	S	Outdoors	Male + Female (twin, Experiment 1) = +50
						Male + Female (twin, Experiment 2) = +420
						Male + Female (twin, Experiment 3) = +320
McCrabb, 1992	England	50%	55 – 95	T	Indoors	Male + Female = -150
Oddy, 1991	Australia	NE	75 – 96	S	Outdoors	Male + Female = -80
						79 – 100

† NE = Non-estimable from the provided information. § days of pregnancy, where 0 (conception) and 150 (-term). * S = Singletons, T = Twin

The late-pregnancy subgroup included two types of experimental set-up: 1) late-pregnancy undernutrition only (i.e. from day 90 to term) or 2) long-term undernutrition that extended into late-pregnancy (Figure 17). Only a few outdoor experiments were usable for meta-analysis, with the majority of studies in this subgroup being undertaken indoors (see Table 6). Overall, undernutrition was associated with a significant decrease in lamb birth weight ($\beta_{[\text{meta-analytic mean}]} = -0.73$, 95% HPD = -0.88 to -0.56). Indoor experiments observed significantly larger effects on birth weight (Figure 17 - black lines; $\beta_{[\text{indoors}]} = -0.85$, 95% HPD = -1.02 to -0.68) than outdoor experiments (Figure 17 - green lines; $\beta_{[\text{outdoors}]} = -0.55$, 95% HPD = -0.82 to -0.34; Supplementary Table S3.4). In addition, a significant, although small publication year effect was found ($\beta_{[\text{Publication year}]} = 0.24$, 95% HPD = 0.10 to 0.40), suggesting that the publication year effect found in the main analysis was largely restricted to this set of studies. No additional predictors had substantive impact on birth weight responses to undernutrition.

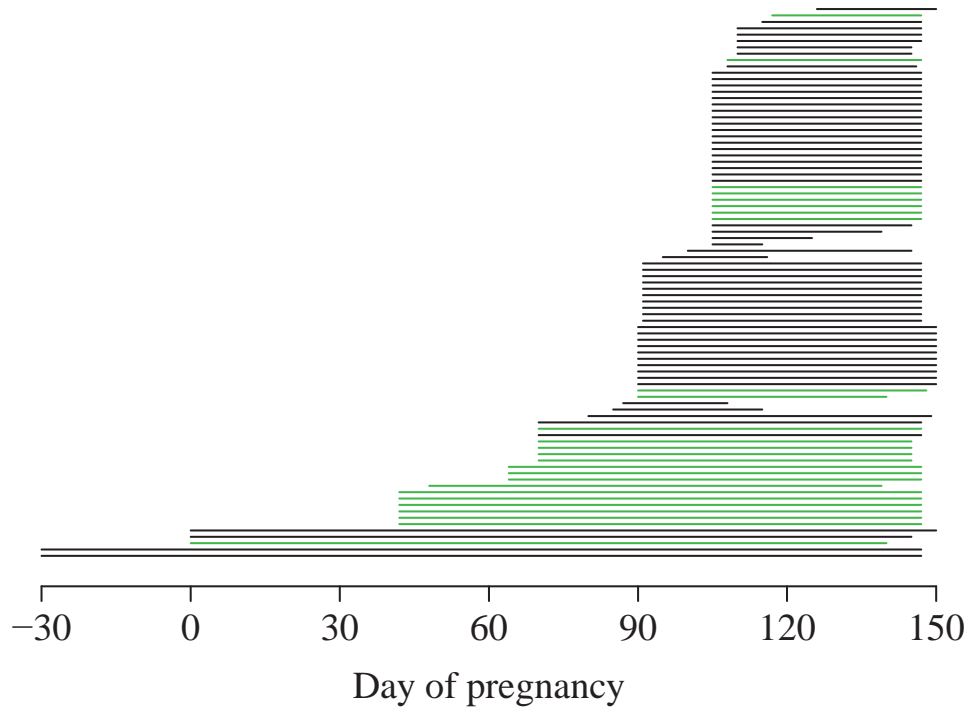


Figure 17. Line plot representing the nutritional manipulations for each observation in the late-pregnancy subgroup. Black and green lines represent nutritional manipulations undertaken indoors or outdoors, respectively.

Table 6. Summary of papers used for meta-analysis in the late-pregnancy subgroup. Liveweight (LW) change refers to the difference in ewe live weight between the commencement of the nutritional treatment and that at the end of the nutritional treatment (including conceptus mass). In studies marked with ^{CF}, liveweight changes are the difference between ewe live weight at the initiation of the nutritional treatment and the post-lambing weight. In studies marked with ^{ML}, liveweight changes are the difference between mating weight and post-lambing weight. The level of undernutrition (relative to pregnancy maintenance, PM) is shown when and as stated by the authors.

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Nordby, 1987	United States	70% - 0 kg	-30 - 147	S and T	Indoors	Single - Male + Females = -600 Twin - Male + Females = -1100
Schinckel, 1961	Australia	NE	0 - 150	S	Indoors	Male + Females = -1340
Short, 1955	Australia	49% - ↓~3.5 kg	0-145	S	Indoors	Male + Females = -1000
Bielli, 2002	Australia	70% - 0 kg	70 - 147	S	Indoors	Male = -670
Olazabal, 2013	Mexico	70% - 0 kg ^{CF}	70 - 147	S and T	Indoors	Twin - Male + Females = -700
Banchero, 2006	Australia	70% - ↓~3.5 kg	80 - 149	S	Indoors	Male + Female = -530
Fahey, 2005	England	50%	85 - 115	T	Indoors	Male + Females = -940
Oddy, 1991	Australia	NS	87 - 108	S	Indoors	Male + Females = -30
Hashemi, 2008	Iran	90% - ↓~0.84 kg ^{CF}	90 - 150	S	Indoors	Male + Females (vs. PM) = -260 Male + Females (vs. 1.1PM) = 0
Hashemi, 2008	Iran	↓~4.30 kg ^{CF}	90 - 150	S	Indoors	Male + Females (vs. PM) = -1020 Male + Females (vs. 1.1PM) = -760

Table 6. continued...

First author, year	Location	Level of restriction / liveweight change †	Period of restriction ‡	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Khalaf, 1979	Scotland	Single: ↓~10.35 kg ^{ML} Twin: ↓~9.81 kg ^{ML}	90 – 150	S and T	Indoors	Single - Male + Females (vs. Medium) = -500 Twin - Male + Females (vs. Medium) = -370 Single - Male + Females (vs. High) = -380 Twin - Male + Females (vs. High) = -950
Cartwright, 1976	Australia	Group 2 - ↓~3 kg Group 3 - ↑~3 kg	91 – 150	S	Indoors	Group 2 - Male + Females = -1230 Group 3 - Male + Females = -620
Sheehan, 1972	Ireland	Silage – singles ↓~3 kg ^{CF} Silage – twins ↓~6.3 kg ^{CF} Silage/12 Barley – twins ↓~5 kg ^{CF} Silage/23 Barley – twins ↓~3.3 kg ^{CF}	91 – 147	S and T	Indoors	Single - Male + Females (vs. Pellets) = -500 (vs. Silage/12Barley) = -500 (vs. Silage/23Barley) = -800 Silage Twin - Male + Females = -800 Silage/12 Barley Twin - Male + Females = -400 Silage/23 Barley Twin - Male + Females = -500
Sheehan, 1977	Ireland	~0 kg	91 – 147	T	Indoors	Experiment 1 Male + Females (vs. Medium) = -600 Male + Females (vs. High) = -500 Experiment 2 Male + Females (vs. Medium) = -600 Male + Females (vs. High) = -400
Oddy, 1991	Australia	NE	95 – 116	S	Indoors	Male + Females = +30
Borwick, 2003	Scotland	70%	100 – 145	T	Indoors	Female = -600

Table 6. continued...

First author, year	Location	Level of restriction / liveweight change †	Period of restriction ‡	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Oliver, 2001	New Zealand	↓7 kg	105 – 115	S	Indoors	Male + Females = -200
Oliver, 2001	New Zealand	↓10 kg	105 – 125	S	Indoors	Male + Females = -600
Mellor, 1985	Scotland	NE	105 – 145	T	Indoors	LP - Male + Females = -840 LP/HP - Male + Females = -990
Husted, 2007	Denmark	50% - 0 kg	105 – 147	T	Indoors	Male + Females = -900
Khantal, 2014	Denmark	50% - ↑4.3 kg	105 – 147	T	Indoors	Male + Females (vs. PM) = -460 Male + Females (vs. 1.5PM) = -490
Kiani, 2011	Denmark	60% - ↓~5 kg	105 – 147	T	Indoors	Male + Females = -400
Kiani, 2008a	Denmark	60% - ↓~3 kg ^{CF}	105 – 147	T	Indoors	Male + Females = -700
Kiani, 2008b	Denmark	60%	105 – 147	T	Indoors	Restricted ewes underfed in early life Male + Females = -300 Restricted ewes adequately fed in early life Male + Females = -450
Louca, 1974	Cyprus	↓~5 kg	105 – 147	S	Indoors	Awassi ewes only - Male + females = -400
Nielsen, 2013	Denmark	50%	105 – 147	T	Indoors	Male + Females = -595
Russel, 1967	Scotland	Group 2 Singles = ↑~2 kg Twins = ↑~6 kg Group 3 Singles = ↑~1 kg Twins = ↑~3.4 kg	105 – 147	S and T	Indoors	Group 2 Single - Male + Females = -300 Twin - Male + Females = -550 Group 3 Single - Male + Females = -1100 Twin - Male + Females = -1400

Table 6. continued...

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Wallace, 1948	New Zealand	LW maintenance				<i>Experiment 1</i>
		↓~0.5 kg	105–147	T	Indoors	LW maintenance - Male + Females = -1443
		Sub-maintenance ↓~6.3 kg				
						<i>Experiment 2</i>
						Male + Females = -1689
Treachler, 1970	England	10% LW gain				
		↓~3 kg ^{CF}	105–147	T	Indoors	10% LW gain - Male + Females = -330
		LW maintenance ↓~7.5 kg ^{CF}				
Norgaard, 2007	Denmark	50% - ↓~15 kg ^{CF}	108–146	T	Indoors	Male + Females = -450
Ojha, 2013	England	60%	110–145	T	Indoors	Male + Females = -200
Sebert, 2011	England	60%	110–145	T	Indoors	Male + Females = -1150
Hyatt, 2007b	England	50%	110–147	T	Indoors	Male + Females = -500
Pearce, 2005	England	50%	110–147	T	Indoors	Male + Females = -400
Yabuku, 2007	England	50%	110–147	T	Indoors	Male + Females = -220
Yabuku, 2007	England	50%	115–147	T	Indoors	Male + Females = -360
Goodchild, 1999	Syria	↑0.5 kg	126–150	S	Indoors	Male + Females = -20
Everitt, 1967	Australia	↓~7 kg	0–140	S	Outdoors	Male + Females = -1231
						Male + Female (single – Experiment 1) = -330
		Exp 1 = ↓~5 kg				Male + Female (single – Experiment 2) = +330
		Exp 2 = ↓~4.5 kg	42–147	S and T	Outdoors	Male + Female (single – Experiment 3) = -310
		Exp 3 = ↓~2.7 kg				Male + Female (twin – Experiment 1) = -280
						Male + Female (twin – Experiment 2) = -50
						Male + Female (twin – Experiment 3) = -410

Table 6. continued...

First author, year	Location	Level of restriction / liveweight change †	Period of restriction §	Litter size *	Housing	Difference in lamb birth weight relative to control (grams)
Kelly, 1996	Australia	↓~8.8 kg	48 – 139	S	Outdoors	Male + Females = -500
Morris, 2004	New Zealand	↓~3 kg ^{CF}	64 – 147	T	Outdoors	Male + Female = -280 (vs. 4 cm) Male + Female = -490 (vs. 6 cm) Male + Female = -570 (vs. 8 cm)
2005 trial:						
Male + Females (vs. 6 cm) = 0						
Kerslake, 2008	New Zealand	2005 = ↑~7 kg	70 – 145	T	Outdoors	Male + Females (vs. 6 cm + concentrate) = -300
		2006 = ↑~10 kg				2006 trial: Male + Females (vs. 6 cm) = 0 Male + Females (vs. 6 cm + concentrate) = -500
Corner, 2008	New Zealand	↑6 kg until day 130	70 – 147	T	Outdoors	Male + Females = -270
Everitt, 1967	Australia	↓~1 kg	90 – 140	S	Outdoors	Male + Females = -872
Cal-Pereyra, 2011	Uruguay	↓~0.23 kg	90 – 148	S	Outdoors	Male + Females = -115
Holst, 1986	Australia	Exp 1 = ↓~2.5 kg Exp 2 = ↓~2 kg Exp 3 = ↓~3 kg	105 – 147	S and T	Outdoors	Male + Female (single – Experiment 1) = -500
						Male + Female (single – Experiment 2) = +180
						Male + Female (single – Experiment 3) = -600
						Male + Female (twin – Experiment 1) = -260
Male + Female (twin – Experiment 2) = -360						
Male + Female (twin – Experiment 3) = -820						
Corner, 2008	New Zealand	↑2.2 kg until day 130	108 – 147	T	Outdoors	Male + Females = -460
Teixeira, 2007	Brazil	NE	117 – 147	S	Outdoors	Male = -680

† NE = Non-estimable from the provided information. § days of pregnancy, where 0 (conception) and 150 (-term). * S = Singletons, T = Twin

3.4.2.2 *Overnutrition*

Only 15 overnutrition studies were deemed acceptable for quantitative analysis (Table 7). A total of 25 observations were extracted from these studies, which were conducted across a time span of 43 years. The extracted data was representative of variations in the duration of overnutrition rather than overnutrition at specific stages of pregnancy (Figure 18). Interestingly, 28% of observations were obtained from studies conducted between 1971 and 1981. The remainder of observation (72%) were obtained from studies undertaken between 2004 and 2014. The major contributing country to this dataset was New Zealand (40%), with the remainder of the records distributed among 8 countries.

Overall, feeding ewes above their PM requirements resulted in a small but significant increase in lamb birth weight ($\beta_{[\text{meta-analytic mean}]} = 0.23$, 95% HPD = 0.002 to 0.48; Supplementary Table S3.5) when compared to PM-fed ewes. Large heterogeneity across study results was observed ($I^2_{\text{total}} = 74.80\%$), and given the few observations available, no individual predictor was able to further explain the residual heterogeneity. Nevertheless, Figure 19 illustrates the difference in effect sizes across studies undertaken indoors and outdoors plotted against their precision. Two points are clear from Figure 19: first, that outdoor experiments are undertaken with larger sample sizes than indoor experiments; and second, that responses have been more variable in outdoor relative to indoor experiments, where the majority of studies have found positive effect on lamb birth weight. Indeed, the meta-regression analysis indicated that, overall, indoor experiments observed a significant increase on lamb birth weight ($\beta_{[\text{indoors}]} = 0.34$, 95% HPD = 0.03 to 0.66), whilst outdoor experiments resulted in a non-significant intercept ($\beta_{[\text{outdoors}]} = 0.13$, 95% HPD = -0.25 to 0.55).

Table 7. Summary of papers used for meta-analysis in the overnutrition dataset. Differences in live weight (LW) gains were calculated as the difference of LW gain/loss between the control and overfed groups between the commencement of the nutritional treatment and that at the end of the nutritional treatment (including conceptus mass). In studies marked with ^{CF}, differences in LW gain were calculated as the difference in ewe live weight between the initiation of the nutritional treatment and the post-lambing weight. In studies marked with ^{ML}, differences in LW gain were calculated as the difference between mating weight and post-lambing weight. The level of overnutrition (relative to pregnancy maintenance, PM; as pasture height; or ewe body condition score, BCS) is shown when and as stated by the authors.

First author, year	Location	Overnutrition level / difference in LW gain	Period of overnutrition δ	Litter size*	Difference in lamb birth weight relative to control (grams)
Long, 2011	United States	1.5PM - \uparrow ~34.6 kg	-60 – 150	S	Male + Female = +800
Ford, 2009	United States	1.5PM - \uparrow ~27 kg	-60 – 148	S	Male + Female = +970
Zhu, 2009	United States		-60 – 148	T	Male + Female = +680
Kenyon, 2011	New Zealand	\uparrow ~3.8 kg	21 – 49	T	Male + Female = -90
Kenyon, 2009	New Zealand	Single - \uparrow ~0.5 kg ^{MT} Twin - \uparrow ~1 kg ^{MT}	21 – 140	S and T	Single - Male + Female = +160 Twin - Male + Female = +710
Kenyon, 2011	New Zealand	\uparrow ~5.2 kg	21 – 140	T	Male + Female = -337
Kenyon, 2011	New Zealand	\uparrow ~4.4 kg	50 – 139	T	Male + Female = -274
Morris, 2004	New Zealand	6cm - \downarrow 0.5 kg ^{CF} 8cm - \downarrow 0.7 kg ^{CF}	64 – 147	T	6cm - Male + Female = +209 8cm - Male + Female = +295
Hashemi, 2008	Iran	1.1PM - \uparrow 0.8 kg ^{CF}	90 – 150	S	Male + Female = -260
Khalaf, 1979	Scotland	Single - \uparrow 13.7 kg ^{MT} Twin - \uparrow ~5.2 kg ^{MT}	90 – 150	S and T	Single - Male + Female = -120 Twin - Male + Female = +580
Banchero, 2004	Uruguay	NE	134 – 149	T	Cracked maize - Male + Female = +500

Table 7. continued...

First author, year	Location	Overnutrition level / difference in LW gain	Period of overnutrition §	Litter size*	Difference in lamb birth weight relative to control (grams)
Hawken, 2012	Australia	NE	134 – 148	T	Calm - Male + Female = +185 Nervous - Male + Female = +830
Kenyon, 2012	New Zealand	BCS2 - ↑3.3 kg	112 – 136	T	CS2 - Male + Female = -200
		BCS2.5 - ↑1.6 kg			CS2.5 - Male + Female = -100
		BCS3 - ↑~3 kg			CS3 - Male + Female = +200
Economides, 1981	Cyprus	Singles - ↑1.3 kg	107 – 152	S and T	Single - Male + Female = -220
		Twins - ↑2.2 kg		T	Twin - Male + Female = +330
Khanal, 2014	Scotland	1.5PM - ↑~4.1 kg	105 – 147	T	Male + Female = +30
Treachner, 1971	England	Single - ↑8.8 kg	105 – 147	S and T	Single - Male + Female = +130
		Twin - ↑6 kg		T	Twin - Male + Female = +360

† NE = Non-estimable from the provided information. § days of pregnancy, where 0 (conception) and 150 (~term). * S = Singletons, T = Twin

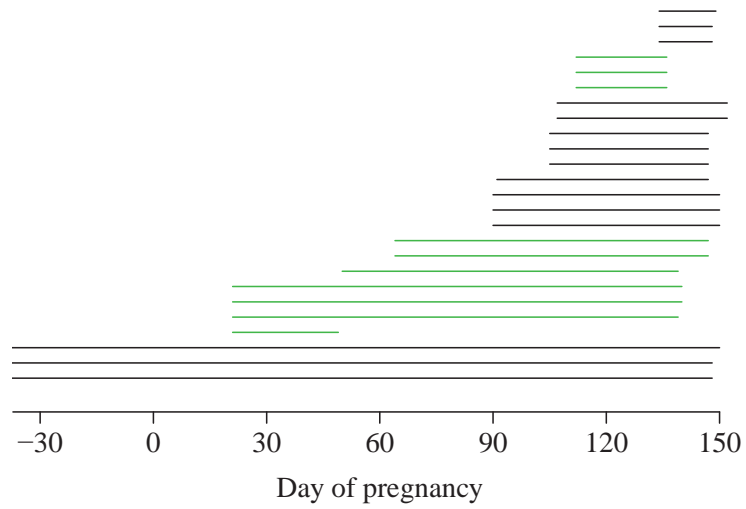


Figure 18. Line plot representing the nutritional manipulations for each observation in the overnutrition dataset. Green and black lines represent studies with nutritional manipulations undertaken outdoors and indoors, respectively.

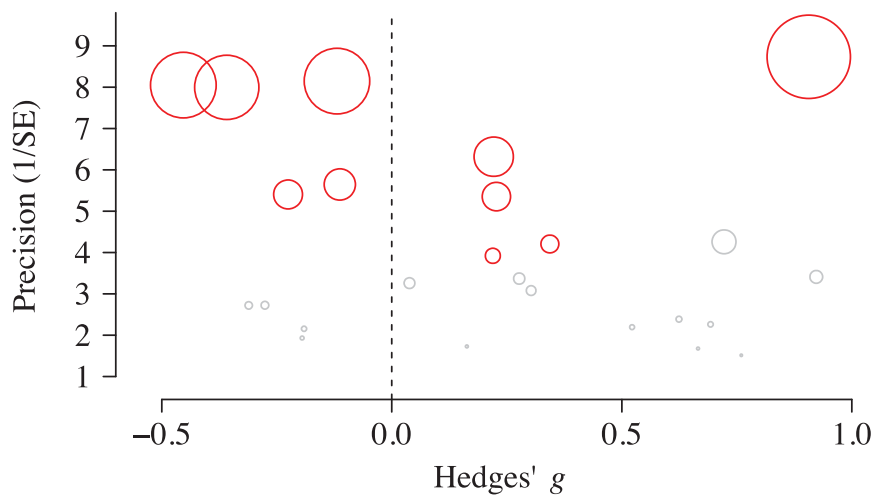


Figure 19. Funnel plot of effect sizes in the overnutrition dataset plotted against their precision (1/standard error). Red and grey bubbles are effect sizes for studies undertaken indoors and outdoors, respectively. Differences in bubble circumference accentuate the differences in sample size between studies.

3.4.3 Publication bias

Visual inspection of funnel plots in the undernutrition dataset (Figure 20a and Figure 20b) indicated evidence of data distribution asymmetry. This was confirmed by a significant intercept of the Egger's regression test ($\beta_{[\text{intercept}]} = -1.24$, 95% HPD = -1.88 to 0.62). Further inspection of publication bias within each subgroup revealed a significant intercept only for the late-pregnancy subgroup ($\beta_{[\text{intercept} - \text{Late}]} = -1.59$, 95% HPD = -2.45 to -0.86). On the contrary, the non-significant intercept of Egger's regression test in the overnutrition dataset indicated little evidence of publication bias ($\beta_{[\text{intercept}]} = 0.09$, 95% HPD = -1.77 to 2.01; Figure 20c and Figure 20d).

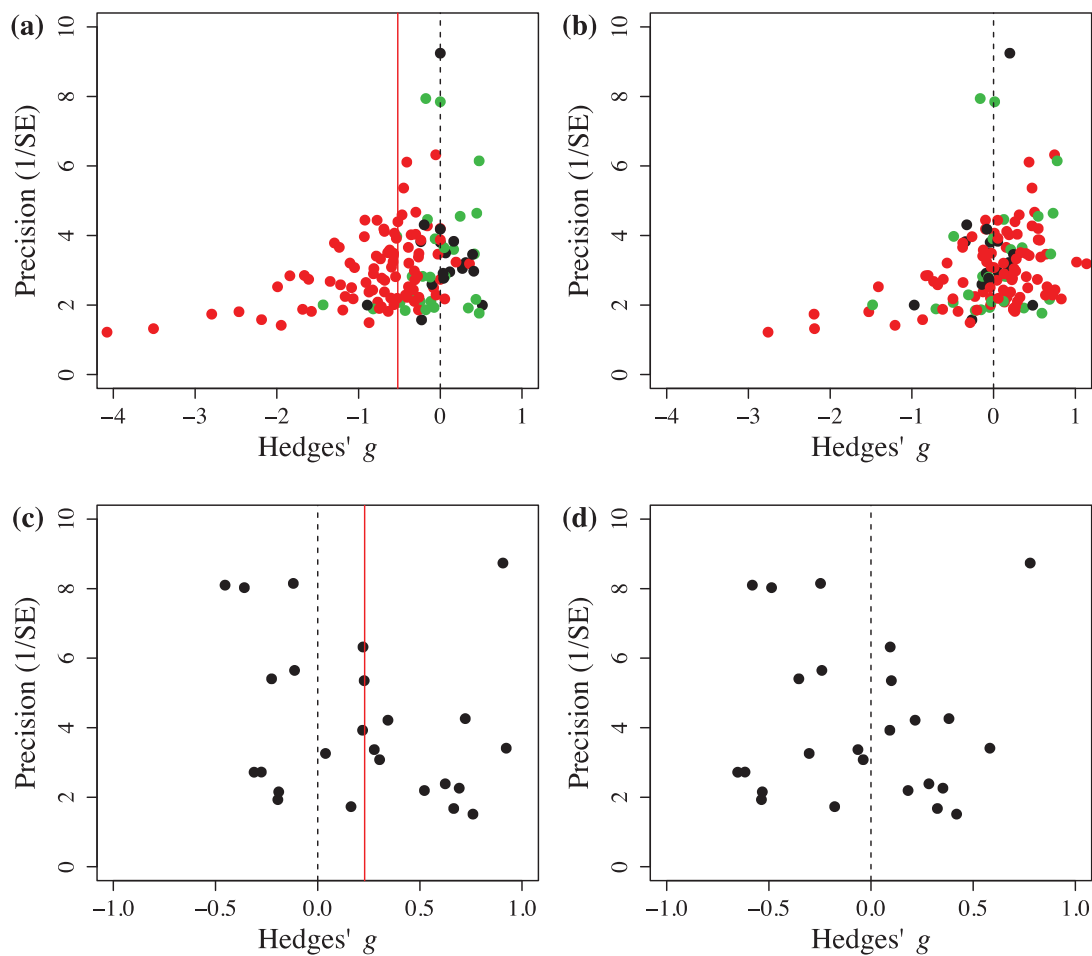


Figure 20. Funnel plots of raw data (a and c) and the residuals and sampling error effects (b and d) from full models in the undernutrition (a and b) and overnutrition (c and d) datasets. Overall posterior (meta-analytic) means are shown as solid lines and zero effect is shown as dashed lines. Observations marked in black, green and red in the undernutrition funnel plots (a and b) depict observations in studies undertaken in early-, mid- and late-pregnancy.

3.4.4 Sensitivity analysis

Two studies were removed since they appeared to have been influencing the effect of late-pregnancy undernutrition: Holst et al. (1986) was excluded from analysis since it introduced a significant amount of non-independence and as it contributed 13% of the effect-sizes in the undernutrition dataset. Wallace, (1948) was also removed due to the exaggerated effect sizes observed, which may have been responsible for the publication year effect estimated in the main analysis. Four more observations were removed from studies having a sample size of 5 or less in either the control or treatment groups (Gardner et al. 2005; Hyatt et al. 2007a; Krausgrill et al. 1999 - Experiment 2 and Nordby et al. 1987 - Twin data).

Results from these sensitivity analyses are shown in Supplementary Tables S3.6 – S3.8. Removing the 25 observations did not influence the pattern of results presented in the main analyses. For example, overall effects were similar than in the main analysis: early-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = 0.03$, 95% HPD = -0.12 to 0.21), mid-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = -0.08$, 95% HPD = -0.28 to 0.11) and late-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = -0.72$, 95% HPD = -0.86 to -0.56). Although, in the late-pregnancy subgroup, the difference in effect size observed between indoor and outdoor experiments in the main analysis was no longer significant in the sensitivity analysis.

Further exploration for publication bias in the late-pregnancy subgroup indicated a significant intercept of Egger's regression on the residuals and measurements errors ($\beta_{[\text{intercept} - \text{Late}]} = -1.36$, 95% HPD = -2.52 to -0.31), suggesting that funnel plot asymmetry

remained present despite the removal of influential observations. In the main analysis, the trim-and-fill tests suggested eight studies missing from the bottom left of the plot (that is, low sample size studies observing a large increase in birth weight as a result of maternal undernutrition in late-pregnancy). After removing influential studies from this subgroup, the trim-and-fill test suggested no missing studies. Given the moderate estimated heterogeneity in this subgroup and the unlikely scenario of late-pregnancy undernutrition having a positive effect on lamb birth weight it is likely that the observed data distribution asymmetry is attributable to the between-study variation (i.e. heterogeneity) rather than true publication bias.

3.5 Discussion

This meta-analysis sought to quantify the variation in birth weight responses to maternal nutrition during pregnancy across 70 studies and to determine the implication this may have for sheep production systems. It was demonstrated that managing the ewe nutrition during late-pregnancy is central to achieving optimum lamb birth weights. Failing to meet the ewe's basic pregnancy nutrition requirements can result in up to a 22% decrease in lamb birth weight. On the contrary, early- and mid-pregnancy undernutrition had no impact on lamb birth weight when nutrition was re-established to adequate levels after the period of restriction. The results in this meta-analysis confirm our hypotheses and provide analytical support to previous narrative reviews (Harding, 2001; Rhind et al. 2001, 2003; Greenwood and Bell 2003; Rhind, 2004; McMillen and Robinson 2005; Bell 2006; Wu et al. 2006; Greenwood and Thompson, 2007; Caton and Hess, 2010; Kenyon and Blair, 2014) and systematic reviews (Rooke et al. 2014). Furthermore, results reported here suggest that lamb birth weights can be increased by providing ewes with feeding levels above their PM

requirements. However, the limited evidence presented in this study suggests only a small effect that may not justify any practical applications for livestock production, especially for grazing systems, but further research is needed.

This meta-analysis found no overall evidence of a major effect of early- and mid-pregnancy undernutrition on lamb birth weight. “Adequate” levels of nutrition during late pregnancy have been suggested to alleviate the effects of early- and mid-pregnancy undernutrition (Greenwood and Thompson, 2007; Kenyon and Blair, 2014; Bell and Greenwood, 2016). In this meta-analysis, studies were selected so that maternal nutrition post treatment was resumed to either PM or above, thereby explaining the lack of observed overall effects. Nonetheless, the lack of a moderating effect from the selected predictors was unexpected since, for example, the duration of the undernutrition period should be a key factor in determining both ewe LW changes and the associated effects on lamb birth weight, especially during severe undernutrition periods. However, information on the level of undernutrition (in the form of ewe LW and BCS loss) is difficult to obtain from these studies. Therefore, the extent of LW loss that ewes can endure before measurable effects are seen on lamb birth weight remains unresolved from the available data.

In the early-pregnancy undernutrition studies included in this meta-analysis (which is limited to only seven studies; Table 4), maternal LW data were not reported in 4 studies. In addition, two studies in which “severe” undernutrition (50% PM) was used had no effect on ewe LW during the restriction period (e.g. Chadio et al. 2007 and Cleal et al. 2007). Results from these studies therefore limit our understanding of the variation in birth weight responses to early-pregnancy undernutrition in relation to changes in the ewe live weight

and/or body condition. Similarly, within the periconceptional undernutrition studies, substantial effects on lamb birth weight were only observed in those studies where undernutrition started 60 days before mating. This observation appears to be due to differences in the pattern of ewe live weight loss between experiments and its effect on the ewe's body reserves at mating. A steady decrease in ewe LW throughout the restriction period (e.g. Debus et al. 2012) or a minor decrease in ewe LW (e.g. Smith, 2010), with minor effects on BCS at mating, resulted in lambs of similar weights to those in the control treatments. On the contrary, lighter lambs at birth were the result of a 15% decrease in ewe LW (~8kg; Oliver et al. 2005). This decrease in LW, however, was achieved within the first 15 days of the restriction period and maintained until day 30 of pregnancy, suggesting that restricted ewes entered mating at a considerably lower LW and BCS compared to controls. The effect of such level of undernutrition was still apparent close to lambing with restricted ewes being ~6 kg lighter than controls. Again, it is difficult to draw conclusion from studies where maternal data were not reported (Hernandez et al. 2009; Jaquiery, 2011, 2012), especially since these results appear to contradict those of Oliver et al. (2005) and more interestingly, reported differential effects on singletons and twins.

No particular pattern in birth weight responses to mid-pregnancy undernutrition arises from the selected studies, which was reflected in the large proportion of variations at the experiment level. This is particularly interesting because observations of the effect of mid-pregnancy undernutrition on placental weight also showed no clear pattern (Luther et al. 2005). The lack of sufficient experimental evidence for meta-analytic use may have obscured the estimation of the true effect of mid-pregnancy undernutrition on lamb birth weight. However, some of the inconsistency in responses across experiments is likely the

result of the low replication rate (that is, the number of experiments undertaken) within a particular feeding regimen, the use of inadequate sample sizes to detect subtle differences in lamb birth weight, the management of the experimental ewes (i.e. indoors vs. outdoors), differences in ewe LW and BCS prior to experimentation and the level of undernutrition. Although, in the lack of enough data for analysis, this requires further investigation.

The level of feeding during late-pregnancy is critical to achieving optimum lamb birth weights and this meta-analysis showed that failing to meet basic pregnancy nutrition requirements resulted in up to a 22% decrease in lamb birth weight. This evidence suggest that farmers should maintain an even plane of nutrition during late-pregnancy (that is, a PM-level of feeding) to avoid any negative effect on lamb birth weight and its associated risks. An important aspect of extensive grazing systems is that some ewes may be under- and overfed regardless of the pasture levels being offered. Therefore, determining the optimum feeding level for late-pregnancy will then depend upon the previous nutritional status of the ewe (e.g. nutritional level during early- or mid-pregnancy or on-farm differences in BCS in the flock).

The larger effect seen in indoor compared to outdoor experiments in the main analysis was no longer observed after the removal of influential studies. The estimated 95% HPD intervals suggests that perhaps the major difference between these two experimental set-ups is the lower bound of birth weight responses being observed (i.e. some outdoor studies observing more mild effects on lamb birth weight). From Figure 17, however, it was clear that the majority of indoor experiments were undertaken exclusively between day 90 of pregnancy and lambing. Whereas, most outdoor experiments were long periods of

undernutrition starting around mid-pregnancy. This suggests an unbalanced nature of the data in relation to the length of undernutrition. In the Chapter 2, the length of undernutrition was found to moderate fetal weight responses across experiments (i.e. more severe responses than just late-pregnancy undernutrition), whilst in the present study this was not the case. This is important because it confirms previous knowledge that different patterns in maternal nutrition during pregnancy can lead to similar effects on lamb birth weight (Harding, 1997a, 1997b). Although, the lack of a moderating effect of the length of undernutrition in the present meta-analysis may be explained by the unbalanced nature of the extracted data.

The publication year effect observed in the late-pregnancy subgroup can be classified as a time-lag bias. The term “time-lag bias” describes the situation in which early published studies show the most inflated results, resulting in a continuously decreasing treatment effect (Ioniddis, 2005). In the present study, this time-lag bias may reflect two scenarios: first, that early research may have been driven towards nutritional manipulations that were significantly effective at reducing lamb birth weight and second, it may also reflect the large changes in accepted animal ethics standards that started in the 1950’s and were subsequently adopted globally in the late 1980’s (Sandoe and Christiansen, 2008), which likely affected the “accepted” levels of feeding restriction in later years.

The literature looking at the effect of maternal overnutrition during pregnancy on lamb birth weight is limited, especially when each stage of pregnancy is considered. Nevertheless, this meta-analysis showed that overnutrition resulted in lambs that were heavier at birth than those from PM-fed dams. From the available literature, however, it is

not possible to determine whether short or long-term overnutrition is responsible for this increase in birth weight. And in addition, data at each individual stage of pregnancy is unavailable, indicating that further work is required.

Two additional points also require discussion: first, in developing nutritional plans that can be applied on-farm, looking at solely the effect on lamb birth weight may neglect other potential effects that undernutrition around this period could have, not only on the ewe and her lambs, but also on the capital return of the farm. Ultimately, farm profitability relies on the number and weight of lambs surviving to weaning (Amer et al. 1999; Morel and Kenyon, 2006). Farmers should avoid severe undernutrition periods, especially if pre-mating nutrition affects live weight and body condition at mating which can negatively affect both conception and lambing rates (Gunn et al. 1991; Yilmaz et al. 2011). Whilst, only minor effects were observed in the early- and mid-pregnancy subgroups, it is important to note that other effects (likely the result of the nutritional treatments) were also observed. Oliver et al. (2005) observed a negative effect on lamb viability (50% of lambs in their nutritional treatment died after birth). Everitt (1967) reported a 38% decrease in lambing percentage compared to controls. Krausgrill et al. (1999) reported that the severe undernutrition in Experiment 2 (i.e. ~15 kg ewe LW loss) resulted in a large number of ewes failing to maintain their pregnancy. Whilst not a complete list, observations like these impose further limitations for this kind of experimentation, because lamb birth weight cannot be measured in pregnancies that are lost and so the true “production” effect of early-to-mid- and mid-pregnancy undernutrition may be underestimated. Second, farmers often rely on periodical measurements of LW and BCS during pregnancy to manage feed allocation. Differences in breeds and nutritional regimens across experiments do not allow

for direct comparison between experiments and therefore, the estimation of an effect-size (which is readily comparable across experiments) is needed. Perhaps, the major limitation from the available literature is the lack of reporting detail or inconsistency of reporting information related to ewe LW and BCS. Often, ewe LW data is either not reported, reported without a measurement of dispersion, presented in illegible graphs (e.g. error bars overlapping across treatments) or is simply not comparable across experiments (e.g. LW change vs LW from mating to lambing vs. LW at start of restriction to post-lambing). Within each subgroup (early-, mid- and late-pregnancy), only four, three and 15 studies had LW data suitable to estimate an effect size, respectively. This represents only 30% of all the included studies. Ewe BCS data were rarely reported in the literature, especially at mating (n = 8 studies out of a total of 70). This restricts their usage for meta-analysis and limits our understanding of how changes in ewe LW and BCS influence lamb birth weight responses across experiments.

3.6 Conclusion

The present meta-analysis represents the first evidence-based effort to quantitatively combine knowledge from studies of maternal nutrition during pregnancy and its effect on lamb birth weight. Undernutrition in early- and mid-pregnancy had only a small and non-significant effect on lamb birth weight. In contrast, late-pregnancy undernutrition and long-term undernutrition extending to late-pregnancy were associated with up to 22% decrease in lamb birth weight. Further, literature on the effect of above PM feeding and its effect on lamb birth weight is limited but this meta-analysis suggests that lamb birth weight can be improved by increasing the ewe's level of feeding above her pregnancy requirements. The combined results from this and the previous meta-analyses indicate that on-farm feeding

management practices should emphasise providing ewes with the nutrients required at each stage of pregnancy. Farmer facing a conflict between feed availability and demand during early- and mid-pregnancy can rely on the ewe's body reserves and allow some live weight loss with relatively no consequence on lamb birth weight if feed supply is adequate later in pregnancy. A feed shortage during late-pregnancy, however, will undoubtedly affect lamb birth weight. So management practice should focus on providing adequate levels of nutrition to those ewes that are at greater risk (i.e. ewes carrying multiples and those in poor body conditions). Future research is required to determine the practical implications of providing ewes with nutrients above those required for pregnancy, especially in determining the interaction between the timing and length of above PM feeding. Additional early- and mid-pregnancy undernutrition evidence is needed to strengthen the findings of this meta-analysis. This can be achieved by improving the publication guidelines of nutritional studies so they can be used for meta-analytic purposes. Ultimately, it is this evidence-based information that will help the development of nutritional guidelines for sheep farmers.

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3.8 Supplementary material for Chapter 3

3.8.1 Supplementary methodology

The following Boolean search was adapted to suit the three selected databases: (sheep OR ovine OR ewe* OR ovis aries) AND (*nutri* OR undernutrition OR overnutrition OR diet* OR *feed* OR calori* OR allowance OR *nourish* OR flushing) AND (periconception* OR maternal OR peri-implantation OR pregnan* OR gest* OR prenatal OR programming OR IUGR OR intergeneration* OR intrageneration*) AND (*weight OR growth OR development OR birth OR lamb* OR newborn OR neonat* OR fetal OR fetus OR foet*)

3.8.2 Supplementary references – list of excluded studies

Adolescent sheep

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3.8.3 Supplementary tables

Table S3.1 Summary of the statistical results of meta-analytic and meta-regression models in the undernutrition dataset. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Model of the undernutrition dataset			
Description	Meta-analytic model	Meta-regression model	Additional model
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	-0.52[-0.73 – -0.33]	–	-0.09 [-0.36 – 0.21]
Early-pregnancy	–	0.04 [-0.22 – 0.28]	–
Mid-pregnancy	–	-0.15 [-0.35 – 0.05]	-0.10 [-0.44 – 0.17]
Late-pregnancy	–	-0.72 [-0.86 – -0.55]	-0.63 [-0.92 – -0.32]
Total days	–	–	0.02 [-0.07 – 0.11]
Litter size	–	–	0.01 [-0.07 – 0.11]
Publication year	–	–	0.21 [0.07 – 0.34]
Random effects	VC	VC	VC
Experiment	0.068	0.024	0.023
Breed	0.100	0.046	0.050
Residual	0.133	0.069	0.069
PCV _[Experiment]	–	65%	66%
PCV _[Breed]	–	54%	50%
PCV _[Residual]	–	48%	48%
I^2_{total}	76.30	–	–
$R^2_{LMM(m)}$	–	41.03%	52.56%
$R^2_{LMM(c)}$	–	70.65%	76.91%
DIC	172.21	93.29	94.93

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.2 Main characteristics of studies included in each subgroup.

Description	Stage of pregnancy*		
	Early-pregnancy	Mid-pregnancy	Late-pregnancy
No. of effect sizes per subgroup	18	27	87
Start of restriction (day post-conception)			
Mean (\pm SD [†])	-25 \pm 27	33 \pm 22	85 \pm 31
Range	-61 – 1	0 – 79	-30 – 126
End of restriction (days post-conception)			
Mean (\pm SD)	28 \pm 8	88 \pm 17	145 \pm 8
Range	7 – 35	49 – 107	108 – 150
Duration of restriction (days)			
Mean (\pm SD)	53 \pm 28	55 \pm 20	60 \pm 32
Range	30 – 91	21 – 95	10 – 177

* Refers to studies ending within each particular stage of pregnancy.

[†] SD, standard deviation

Table S3.3 Summary of the statistical results of meta-analytic and meta-regression models in the mid-pregnancy undernutrition subgroup. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the Mid-pregnancy subgroup	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.07[-0.27 – 0.16]	-0.07[-0.27 – 0.13]
Control group	–	-0.12 [-0.27 – 0.03]
Random effects	VC	VC
Experiment	0.091	0.073
Residual	0.013	0.013
PCV _[Experiment]	–	20%
PCV _[Residual]	–	0%
I^2_{total}	52.10%	–
$R^2_{\text{LMM}(m)}$		14.62%
$R^2_{\text{LMM}(c)}$		86.61%
DIC	-57.56	-57.30

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.4 Summary of the statistical results of meta-analytic and meta-regression models in the late-pregnancy undernutrition subgroup. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the late-pregnancy subgroup	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.73[-0.88 – -0.56]	-
Indoors (intercept)	–	-0.85 [-1.02 – -0.68]
Outdoors (intercept)	–	-0.55 [-0.82 – -0.34]
Publication year	–	0.24 [0.10 – 0.40]
Random effects	VC	VC
Experiment	0.117	0.055
Residual	0.103	0.110
PCV _[Experiment]	–	53%
PCV _[Residual]	–	-7%
I^2_{total}	67.00%	
$R^2_{GLMM(m)}$		34.02%
$R^2_{GLMM(c)}$		55.85%
DIC	89.70	93.58

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.5 Summary of the statistical results of meta-analytic and meta-regression models in the overnutrition dataset. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the overnutrition dataset	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	0.23[0.002 – 0.48]	-
Indoors	-	0.34 [0.03 – 0.66]
Outdoors	-	0.13 [-0.25 – 0.55]
Total days		
Random effects	VC	VC
Experiment	0.108	0.110
Residual	0.065	0.066
PCV _[Experiment]	-	-1.8%
PCV _[Residual]	-	-1.5%
I^2_{total}	74.80%	-
$R^2_{\text{LMM}(m)}$	-	11.60%
$R^2_{\text{LMM}(c)}$	-	66.73%
DIC	5.96	7.13

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.6 Summary of the statistical results of the sensitivity analysis of the undernutrition dataset. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the undernutrition dataset – Sensitivity analysis	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.48[-0.67 – -0.32]	–
Early-pregnancy	–	-0.05 [-0.19 – 0.28]
Mid-pregnancy	–	-0.21 [-0.43 – 0.01]
Late-pregnancy	–	-0.69[-0.83 – -0.54]
Random effects	VC	VC
Experiment	0.062	0.013
Breed	0.057	0.025
Residual	0.110	0.071
PCV _[Experiment]	–	79%
PCV _[Residual]	–	56%
PCV _[Residual]	–	35%
I^2_{total}	71.03%	–
$R^2_{\text{LMM}(m)}$		44.53%
$R^2_{\text{LMM}(c)}$		63.94%
DIC	117.25	77.11

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.7 Summary of the statistical results of the sensitivity analysis of the mid-pregnancy undernutrition subgroup. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the Mid-pregnancy subgroup – Sensitivity analysis	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.08[-0.28 – 0.11]	-0.08[-0.28 – 0.12]
Control group	–	-0.11 [-0.26 – 0.04]
Random effects	VC	VC
Experiment	0.091	0.078
Residual	0.013	0.013
PCV _[Experiment]	–	14%
PCV _[Residual]	–	0%
I^2_{total}	53.04%	–
$R^2_{LMM(m)}$		13%
$R^2_{LMM(c)}$		87.76%
DIC	-55.66	-55.22

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Table S3.8 Summary of the statistical results of the sensitivity analysis of the late-pregnancy undernutrition subgroup. 95% highest posterior density (HPD) intervals excluding zero can be considered statistically significant (marked in bold text).

Description	Models of the late-pregnancy subgroup – Sensitivity analysis	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.72[-0.86 – -0.56]	-
Indoors (intercept)	–	-0.77 [-0.92 – -0.61]
Outdoors (intercept)	–	-0.64 [-0.92 – -0.38]
Publication year	–	0.18 [0.05 – 0.33]
Random effects	VC	VC
Experiment	0.043	0.023
Residual	0.123	0.115
PCV _[Experiment]	–	46%
PCV _[Residual]	–	6%
I^2_{total}	57.61%	
$R^2_{GLMM(m)}$		21.66%
$R^2_{GLMM(c)}$		35.34%
DIC	89.70	80.81

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

Chapter 4: Weaning weight is affected by maternal nutrition during pregnancy – a meta-analysis of studies in adult sheep.

4.1 Abstract

Twenty-four studies were deemed acceptable for meta-analysis after a systematic search of studies examining the effect of maternal nutrition during pregnancy on lamb weaning weight. Hedges' g was used to summarise the effects across studies and represent the standardised mean difference in weaning weight between the experimental and the control groups. This meta-analysis indicates that undernutrition during the first 100 days of pregnancy had no significant overall effect on lamb weaning weights (-0.08, 95% highest posterior density (HPD) interval = -0.42 to 0.18). Even when significant negative effects were observed (as undernutrition approached day 100 of pregnancy), these were small in magnitude (-0.27, HPD = -0.48 to -0.08). Undernutrition during late-pregnancy, however, significantly reduced lamb weaning weight (-0.60, HPD = -0.80 to -0.40), with extended periods of undernutrition further reducing lamb weaning weight (-0.29, HPD = -0.50 to -0.11). These results suggest that farmers should aim to maintain a pregnancy maintenance level of feeding during the first 100 days of pregnancy and prioritize the feeding of ewes in poor body condition and those bearing multiples, if a conflict between feed demand and availability is envisioned during late-pregnancy. Increasing lamb weaning weight by feeding ewes above their pregnancy maintenance requirements may be possible in some circumstances, but literature is scarce in this matter and effects are yet to be identified. So far, the estimated overall effect might be too small (0.25, HPD = 0.01 to 0.45) to warrant any practical application, but further research is needed to determine if an interaction exist between the timing and length of above pregnancy maintenance feeding in adult ewes that can result in a sufficient increase in lamb weaning weights so that productivity is improved.

Key words: meta-analysis, weaning weight, sheep, maternal nutrition

4.2 Introduction

Farm profitability is a function of many factors that involved management decisions, external sources (i.e. market price) and production parameters (Nudell et al. 1998; Amer et al. 1999; Morel and Kenyon, 2006; Young et al. 2011). Production parameters such as the number of lambs surviving to weaning (Amer et al. 1999) and their growth rate (Morel and Kenyon, 2006) are important for profitability in a sheep enterprise. Lamb growth to weaning is largely determined by milk intake (Doney and Peart, 1976; Snowder and Glimp, 1991). The ewe's milk production is influenced by her nutrition in pregnancy and during lactation (Caton and Hess, 2010), with the nutrition during lactation having a greater influence (Thompson et al 2011). When nutritional and environmental conditions are optimal from birth to weaning, the effects of pregnancy nutrition are small and only apparent during the first days post-lambing (Mellor, 1983, 1988; Greenwood et al. 2010; Bell and Greenwood, 2016).

There is difficulty in separating the cumulative effects of pregnancy and lactation nutrition in studies where lambs are reared by the dam (Allden, 1970, Greenwood et al. 2010, Kenyon and Blair, 2014). The difficulty in interpretation arises from the confounding effects of post-treatment feeding in late pregnancy, milk production of the dam and milk intake (Greenwood and Thompson, 2007; Greenwood et al. 2010; Caton and Hess, 2010). The need of a standard rearing method to be used in mechanistic studies has been advocated (Greenwood et al. 2010; Kenyon and Blair, 2014) to be able to separate these effects. Although, Kenyon and Blair (2014) argued that studies should allow for the lamb to be reared by its dam if results are to be applicable to commercial conditions.

The influence of the ewe nutrition during pregnancy on the growth of lambs until weaning has been previously reviewed using traditional (Greenwood and Thompson, 2007; Caton and Hess, 2010; Greenwood et al. 2010; Kenyon and Blair, 2014; Bell and Greenwood, 2016) and systematic methods (Rooke et al. 2015). The combined evidence across these reviews suggests that long-term and late-pregnancy undernutrition is associated with decreased lamb growth to weaning (Kenyon and Blair, 2014; Rooke et al. 2015; Bell and Greenwood, 2016). On the contrary, undernutrition around early- and mid-pregnancy has had more variable impacts, but on balance it has been concluded that it has little impact on lamb growth and live weight to weaning (Greenwood and Thompson, 2007; Kenyon and Blair, 2014; Rooke et al. 2015). This is likely because even when undernutrition is sufficient to cause any effects on fetal growth before late gestation, effects can be alleviated by providing adequate nutrition to the dam in late pregnancy, with relatively no consequences for post-natal growth (Greenwood and Thompson, 2007; Kenyon and Blair, 2014; Bell and Greenwood, 2016). Narrative reviews (Bell and Greenwood, 2016; Kenyon and Blair, 2014) have also noted that providing ewes with levels of nutrition above their pregnancy requirements has little impact on the lamb's growth to weaning, likely because the dam takes up the additional nutrition to increase her body reserves rather than increasing the flow of nutrients to the fetus.

This current knowledge, however, have only focused on three experimental factors that create inconsistency in responses across nutritional experiments (i.e. timing, length and severity of undernutrition) and thus, other potential causes of variation across studies remain poorly understood. In addition, the traditional methods used to synthesise the available evidence have only allowed for dichotomous conclusion (i.e. effect or no effect).

Therefore, quantitative synthesis is necessary to provide further support to the current knowledge. The present study used a meta-analytic approach to review the literature of maternal nutrition during pregnancy and its effect on weaning weight. Meta-analysis combines the knowledge obtained from many experimental studies, quantifies the variability in study outcomes and estimates treatment effects across multiple studies. This approach may provide new insights about the optimum nutrition of the pregnant ewe, and more importantly, meta-analytic estimates can then be used as reference points to provide more thorough farm advice. The hypothesis tested in this study was that when ewes are fed to meet their requirements in lactation (i.e. maintenance + lactation requirements or above), long-term and late-pregnancy maternal undernutrition would result in decreased weaning weights irrespective of the weaning age; whereas early- and mid-pregnancy undernutrition and overnutrition of adult ewes would have no impact.

4.3 Material and methods

Integrating the results from many studies require that systematic reviews and meta-analyses are conducted rigorously. Adhering to standard methodological guidelines, therefore, assures editors, reviewers and readers that these reviews have been carefully undertaken. Such guidelines have not yet been developed in Animal Sciences. However, numerous protocols currently exist in the Health and Social Sciences, which can be easily adapted to suit the need of Animal Science meta-analyses. The present study followed, where possible, the “Preferred Reporting Item for Systematic Reviews and Meta-analyses” statement (PRISMA, Moher et al. 2009). The PRISMA statement is an evidence-based set of items for reporting systematic reviews and meta-analyses and provides a 27-item check list that describes the minimum set of information needed for a critical appraisal of published

literature. A four-phase diagram is also a requirement which is used to visually assess the author's judgment in regards of literature search and final inclusion and exclusion decisions.

4.3.1 Search strategy and selection criteria

To identify relevant studies for this meta-analysis, an initial search was conducted in three online databases (i.e. PubMed, SCOPUS and Web of Knowledge) on December 1, 2015. The following search algorithm was used to retrieve all available literature: (sheep OR ovine OR ewe* OR "ovis aries") AND (nutri* OR diet* OR *feed* OR *allowance OR IUGR OR periconception* OR peri-implantation) AND (gest* OR pregnan* OR prenatal OR maternal) AND ("birth" OR "weaning") AND (weight OR mass OR growth OR development OR size) NOT (adolescent OR chicken OR pig OR rat OR mice OR goat OR calf). This algorithm was first established in PubMed and then formatted to suit each individual database. There were no restrictions based on publication date or language in this initial search.

All experimental and review articles were further scrutinized for papers cited and papers citing (i.e. forward and backward searches, respectively) in an attempt to find potentially relevant studies that were not found by the initial search. Titles and abstracts were first reviewed and duplicates were removed. All remaining experimental articles were then fully assessed for eligibility based on information obtained from the main text and graphs, supplementary material or information obtained directly from the authors. Relevant studies investigating the effect of ewe nutrition during pregnancy on lamb weaning weight were eligible for inclusion in this study. To be eligible for meta-analysis, studies had to be

undertaken using adult, multiparous ewes. In addition, studies must have included the following data: 1) the breed of sheep used for experimentation; 2) detailed information about the nutritional manipulations during pregnancy (periconceptional and flushing periods included); 3) the mean weaning weights for each individual treatment and their corresponding measurements of dispersion; 4) litter size and birth weight statistics for each individual birth type and 5) the number of lambs in each individual treatment. In addition to this minimum set of information, an additional constraint was imposed in order to rule out effects of poor nutrition during lactation on the growth of lambs up to weaning. To be eligible for meta-analysis, studies had to have provided ewes with adequate nutrition during lactation; that is, feeding levels to meet requirements for ewe live weight and lactation or above.

Studies failing to comply with these inclusion / exclusion criteria were excluded from this study. If essential information (e.g. sample size, litter size) was missing from the articles, authors were contacted by e-mail, which contained a brief description of the study, specification of the data needed and a request for unpublished data. If adequate clarification or data could not be provided, studies were excluded. Further, studies examining the effect of pregnancy nutrition on adolescent ewes (7 to 10 months of age at breeding), nulliparous ewes (first lambing regardless of age) and triplet-bearing ewes were also excluded. Lastly, cohort studies of previously reported experiments were excluded.

4.3.2 Data extraction

Data from eligible studies were extracted from information presented as text, tables or figures. Relevant information presented as figures was extracted using GraphClick

(Arizona-Software, Los Angeles, CA, USA; Boyle et al. 2013). The main data extracted from each study included name of first author, year of publication, location, average age of the experimental animals, starts and end day (i.e. day of pregnancy) when the nutritional manipulation happened, diet type, whether the control group was fed at pregnancy maintenance (PM) or above levels (i.e. control type), litter size, housing type (i.e. indoors or outdoors), whether lambs were straight- (dam and ram of same breed) or crossbred (dam and ram of different breed), number of lambs at weaning in each treatments, weaning age and weaning weights (mean and standard error; SE).

4.3.3 Data coding and datasets

A study identifier was given to each individual data point. Since there were many studies where multiple treatments were compared to a common control group, each data point was given a second identifier (e.g. control group ID) to account for possible correlated structures within the data. The level of feeding of the control group was coded as either being PM or above PM requirements (WF – well fed). Where authors stated the level of feeding of the control groups, this was adopted. However, when this information was not available, the level of feeding was estimated from the ewe live weight data provided in the study. In the present study, the term “pregnancy maintenance requirements” is defined as the amount of energy required to maintain ewe net live weight throughout pregnancy, whilst allowing for adequate growth of the fetus (or fetuses) at each individual stage of pregnancy. Any nutritional manipulation below and above this threshold is referred to as undernutrition or overnutrition, respectively. Lastly, an additional variable was coded to separate the effects across different stages of pregnancy. In the previous meta-analysis, the data were divided in studies undertaken in early- mid- and late-pregnancy. However, given

the limited number of studies in this meta-analysis, only two periods were considered: Period 1 represented studies with nutritional manipulations during the first 100 days of pregnancy, whereas Period 2 included all studies with nutritional manipulations that either happened during late-pregnancy (between day 90 of pregnancy and term) or that extended into late-pregnancy (i.e. long term nutritional manipulations finishing after day 90 of pregnancy).

Two main datasets were created using the extracted information from the selected studies:

1) the undernutrition dataset contained data involving the comparison between experimental ewes fed below PM requirements and a control-fed group (i.e. either PM-fed or above). 2) The overnutrition dataset compared only an experimental group fed above their PM requirements (i.e. overfed group) versus a control group of ewes fed to meet their PM requirements.

4.3.4 Statistical analysis

This study used Hedges' g as the main effect-size metric for statistical analyses. Hedges' g represents the standardised mean difference in weaning weight between the experimental and the control groups, in terms of the pooled standard deviation and with a small sample size correction (Hedges, 1981). Positive values of Hedges' g can be interpreted as an increase in weaning weight in the experimental groups as a result of a nutritional treatment relative to the weaning weight of the control lambs. A negative effect can therefore be interpreted as a decrease in lamb weaning weight relative to the control lambs.

All statistical analyses were performed using R v.3.0.2 (R Core Team, 2013). Datasets were analysed independently using Bayesian multilevel mixed-effects meta-analysis as implemented in the MCMCglmm package (Hadfield, 2010; Hadfield and Nakagawa, 2010). Two models were used to summarise the mean effect across studies (i.e. traditional meta-analysis) and to explore possible source of heterogeneity (i.e. meta-regression):

Model I: was constructed as an intercept-only model. For the undernutrition dataset, Model I included the random effects of ewe breed and experiment identity. In the overnutrition dataset, only experiment identity was used as a random effect. These meta-analytic models can be written as (following notation by Gelman and Hill, 2007; Nakagawa and Santos, 2012):

$$g_i = \alpha + s_{j[i]} + b_{k[i]} + e_i + m_i,$$

$$\mathbf{s} \sim N(\mathbf{0}, \sigma_{exp}^2 \mathbf{I}),$$

$$\mathbf{b} \sim N(\mathbf{0}, \sigma_{breed}^2 \mathbf{I}),$$

$$\mathbf{e} \sim N(\mathbf{0}, \sigma_e^2 \mathbf{I}),$$

$$\mathbf{m} \sim N(\mathbf{0}, \mathbf{M}),$$

where g_i is the observed effect-size, α is the overall intercept or meta-analytic mean, $s_{j[i]}$ denotes the experiment-specific effect for the j th experiment ($j = 1, \dots, N_{experiment}$) applied to the i th effect size ($i = 1, \dots, N_{effect-size}$; $N_{effect-size}$ is the number of effect-sizes), \mathbf{s} is a 1 by $N_{experiment}$ vector, which is normally distributed around 0 with the between-experiment variance of σ_{exp}^2 (which was unknown but estimated from the data), $\mathbf{0}$ is a 1 by $N_{experiment}$ vector of 0 and \mathbf{I} is the $N_{experiment}$ by $N_{experiment}$ identity matrix; $b_{k[i]}$ (only used in the

undernutrition meta-analysis) is the breed-specific effect for the k th breed ($k = 1, \dots, N_{breed}$; ; N_{breed} is the number of breeds) applied to the i th effect size estimate, and \mathbf{b} is a 1 by vector of b_j , which is normally distributed around 0 with breed-specific variance of σ_{breed}^2 (which was unknown but estimated from the data); e_i is the within-experiment effect for the i th effect-size, and \mathbf{e} is a 1 by $N_{experiment}$ vector of e_j , which is normally distributed around 0 with the within-experiment variance of σ_e^2 (which was unknown but estimated from the data). Lastly, m_i is the sampling error effect for the i th effect-size, \mathbf{m} is a 1 by $N_{experiment}$ vector of m_j , which is normally distributed around 0 with the typical sampling error variance of σ_m^2 (see details in “heterogeneity” section as to how this was estimated), and \mathbf{M} is a $N_{experiment}$ by $N_{experiment}$ matrix, with its diagonal elements being σ_m^2 , which is assumed to be known.

Model II: was constructed as a mixed model that incorporated predictor variables that could explain the variation in results. These meta-regression models were given by:

$$g_i = \theta_i + s_{j[i]} + b_{k[i]} + e_i + m_i,$$

$$\theta_i = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} \dots \beta_n x_{nj},$$

where β_0 is the intercept, $\beta_{1\dots n}$ are regression coefficients and represent the change in effect-size for unit increase in x , with $x_{1\dots n}$ being the values for the predictor variables (where $j = 1 \dots N_{experiment}$). All other symbols are the same as above. In this study, the predictor variables tested were: i) level of nutrition of the control group (undernutrition dataset only), ii) litter size (coded as a binary variables with 1 being singletons and -1 for

twins), iii) duration of undernutrition (total days) iv) undernutrition start day, v) end day, vi) period of undernutrition, which corresponded to a two-level categorical variable (Period 1 and Period 2), vii) housing type and viii) year of study publication. Continuous variables were *z*-scaled, and thus their regression coefficients can be interpreted as the amount of change in effect-size when the predictor variable changes by one standard deviation (SD).

Interdependence of effect sizes arising from multiple treatment groups being compared to a common control group was statistically controlled for by estimating variance and covariance values adjusted for the presence of a common control group using the methods reported by Gleser and Olkin (2009). The calculated variance-covariance matrix of the shared control group identities was incorporated into the statistical models. Random effects were run with the parameter expanded inverse-Wishart prior (the parameter settings in MCMCglmm: $V = 1$, $\nu = 0.002$, $\alpha.\mu = 0$, $\alpha.V = 1000$) and we used the default prior (i.e. a diffuse, non-informative prior) for fixed effects. For each model, three independent Markov Chain Monte Carlo (MCMC) chains were run for 130,000,000 iterations with a thinning of 1,000,000 after 30,000,000 iterations of burn-in. Assessment of model convergence and mixing within chains was examined using the Gelman-Rubin statistic (Gelman and Rubin, 1992) and autocorrelation within chains, respectively. The chain with the lower deviance information criterion (DIC) was chosen to obtain information regarding the posterior mode, mean, standard deviation and 95% highest posterior density (HPD) intervals for meta-analytic model intercepts and predictor slopes. Estimates with 95% HPD interval that did not include zero were considered statistically significant.

4.3.4.1 Heterogeneity

The greatest benefit of conducting a meta-analysis relies on the understanding of the nature of variability in studies and being able to distinguish between different sources of this variation. An extended version of the I^2 index (see Nakagawa and Santos, 2012; cf. Cheung, 2014) is used in this study to describe the percentage of variation in effect sizes across studies that is not attributed to sampling variance, and was calculated as:

$$I^2 = \frac{\sigma_t^2 - \sigma_m^2}{\sigma_t^2} \times 100$$

where σ_t^2 is the sum of all variance components and σ_m^2 is the typical sampling error variance, which can be defined as:

$$\sigma_m^2 = \frac{\sum_{i=1}^k w_i (k-1)}{(\sum_{i=1}^k w)^2 - \sum_{i=1}^k w_i^2}$$

where w_i is the inverse of the i th measurement error variance associated with the i th g estimate ($i = 1, \dots, k$).

In the UN dataset, σ_t^2 was defined by:

$$\sigma_t^2 = \sigma_{exp}^2 + \sigma_{breed}^2 + \sigma_e^2 + \sigma_m^2$$

whereas in the ON dataset and undernutrition subgroups, it was defined by:

$$\sigma_t^2 = \sigma_{exp}^2 + \sigma_e^2 + \sigma_m^2$$

where σ_{exp}^2 is the experiment-level variance, σ_{breed}^2 is the dam breed-level variance, σ_e^2 is the residual variance. Therefore, the proportion of variance at each random effect in relation to the total sum of variance components is $\sigma_{exp}^2/\sigma_t^2$ and is $\sigma_{breed}^2/\sigma_t^2$, respectively.

4.3.4.2 R^2 for meta-regression models

To assess the contribution that the potential predictor variables (i.e. fixed effects), and the selected random factors, had on explaining the variation in responses across studies, two R^2 statistics were calculated, as suggested by Nakagawa and Schielzeth (2013). First, the marginal R^2 denotes the variance explained by the fixed effects as a proportion of the sum of all variance components, and was defined as:

$$R_{LMM(m)}^2 = \frac{\sigma_f^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

where σ_f^2 is the variance attributable to the fixed effects, σ_l^2 is the variance component of the l th random factor, σ_e^2 is the residual variance. Note that σ_m^2 is not part of the formula, as it is considered to be explained already. Second, the conditional R^2 determines the variance explained by fixed and random factors, and was calculated by integrating into the numerator the variance explained by the random factors:

$$R_{LMM(c)}^2 = \frac{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2}{\sigma_f^2 + \sum_{l=1}^u \sigma_l^2 + \sigma_e^2}$$

4.3.4.3 Publication bias

Finding and assessing all studies that meet particular inclusion criteria may not always be possible in meta-analysis. This is because studies with “significant” or interesting results are more likely to be published or promoted than those observing nonsignificant or negative results (Rothstein et al. 2005, Lean et al. 2009). In meta-analysis, this is referred to as publication bias. In the present study, the potential for publication bias was examined using visual inspection of data distribution asymmetry around meta-analytic means in funnel plots (Light and Pillemer, 1984, Rothstein et al. 2005). In addition, funnel plot asymmetry

was evaluated using Egger's linear regression test (Egger et al. 1997). As suggested by Nakagawa and Santos (2012), Egger's regression approach was applied to data points consisting of the residual and sampling errors from the meta-regression models.

4.3.4.4 Sensitivity analysis

The trim-and-fill method (Duval and Tweedy, 2000) was used to adjust the estimates for potential publication bias. The trim-and-fill method assesses asymmetry in the funnel plot and imputes the number of suspected missing studies. The adjusted result can be used as sensitivity analysis to indicate the extent to which publication bias may have affected the results from this study.

4.4 Results

4.4.1 Study retrieval and selection strategy

The search strategy and study selection process are presented in the PRISMA flow diagram in Figure 21. The literature search identified 2856 papers and an additional five papers were found after reviewing the reference lists of 80 key reviews. A total of 2649 papers were then discarded as not being relevant to the research question. Two-hundred and nineteen studies were examined in detail, however, 195 did not meet the inclusion criteria (4.8.2 Supplementary references - list of excluded studies) for the following reasons: studies were undertaken in adolescent or nulliparous sheep (n = 12), weaning weights were reported as the combined weight across various litter sizes (n = 20), or did not have a measurements of dispersion (n = 30), studies reported on a subsample of animals from a previous study (n = 34), the experimental design did not allow the hypothesis of this study to be tested (n = 20) and some key information (i.e. sample size, litter size, interactions) was missing (n = 79).

Authors from seven studies were contacted and five provided either written clarification regarding their experiment or the original experimental data. No unpublished or other relevant data was obtained for this study. Twenty-four studies were subsequently identified as suitable for meta-analysis and represented two major experimental set-ups: relative undernutrition (n = 22) and overnutrition (n = 6). Some studies reported information on both experimental set-ups.

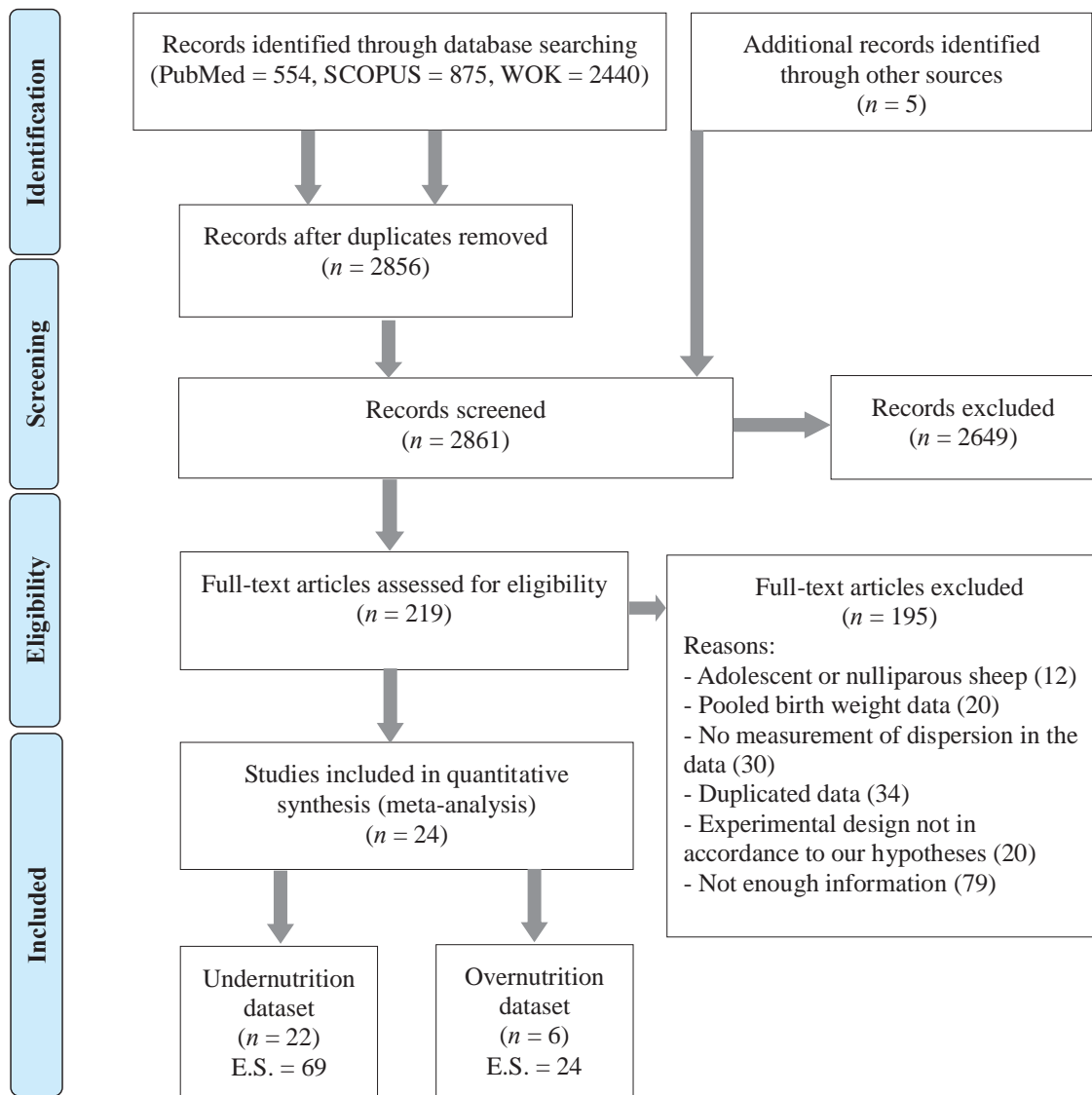


Figure 21. Flow diagram of studies identified, excluded and included in the present study. The number of studies in each category are shown in parenthesis. The number of effect-sizes (E.S.) are given for each dataset.

4.4.2 Study characteristics and meta-analysis

4.4.2.1 Undernutrition

A summary of the studies included in the undernutrition dataset is presented in Table 8 and their main characteristics are provided in Supplementary Table S4.1. Sixty-nine effect sizes (E.S.) were extracted from 22 relevant undernutrition studies. Of these, eight studies (E.S. = 28) reported weaning weights from lambs born to ewes that were undernourished in early- and/or the mid-pregnancy period (i.e. undernutrition ended before day 100 of pregnancy), whilst 15 studies (E.S. = 41) reported lamb data obtained from ewes that were undernourished during late-pregnancy or that were exposed to long-term undernutrition periods that extended into late-pregnancy (see Figure 22). Over all the studies analysed, undernutrition during pregnancy decreased lamb weaning weight ($\beta_{[\text{meta-analytic mean}]} = -0.45$, 95% HPD = -0.77 to -0.17). However, moderate heterogeneity in weaning weight responses across studies was identified ($I^2_{\text{total}} = 66.50\%$, $I^2_{\text{between-experiments}} = 36.50\%$, $I^2_{\text{between-breeds}} = 17.80\%$ and $I^2_{\text{residual}} = 12.10\%$) and thus possible sources for this heterogeneity were explored using meta-regression.

Table 8. Summary of papers used for the undernutrition meta-analysis. Liveweight change is the difference in ewe live weight between the initiation of the nutritional treatment and the ewe live weight at the end of the nutritional treatment (including conceptus mass for studies in late-pregnancy). In studies marked with ^{CF}, live weight differences are the difference between ewe live weight at the initiation of the nutritional treatment and the post-lambing weight. Where available, the energetic level of undernutrition (relative to maintenance) is shown as stated by the authors. For some studies, the level of undernutrition was non-estimable (NE) from the available information. Period of restriction refers to days of pregnancy (0 = conception and ~150 = term).

First author, year	Location	Level of restriction / live weight change	Period of restriction	Difference in lamb birth weight relative to control (grams)
Jaquier, 2011	New Zealand	NE	-61 – 30	Male (single) = +800 Female (single) = +400 Male (twin) = +1500 Female (twin) = +1900
Jaquier, 2012	New Zealand	NE	-61 – 30	Male (single) = 0 Female (single) = -1000
Debus, 2012	France	50% - ↓~5.2 kg	-15 – 30	Male (single) = -1180 Female (single) = -980 Male (twin) = +1340 Female (twin) = +2040
Jaquier, 2012	New Zealand	NE	-2 – 30	Male (single) = -2000 Female (single) = -3000
Kotsampasi, 2009	Greece	50% - ↓~0.6 kg	0 – 30	Male (twin) = -1300 Female (twin) = -400
Cleal, 2007	England	50% - ↑~0.8 kg 50% - ↑~0.6 kg	0 – 30	Male (single) = +2000 Female (single) = +800 Male (twin) = +2700 Female (twin) = -1800
Kenyon, 2011	New Zealand	↓~5.2 kg	21 – 49	<i>Versus MM-group</i> Male (twin) = -100 Female (twin) = -640 <i>Versus HH-group</i> Male (twin) = +110 Female (twin) = -60
Burt, 2007	United States	50% - ↓~6.2 kg	28 - 78	UW ewes - Female = -1810 Baggs ewes - Female = -4300
Everitt, 1967	Australia	↓~8 kg	0 – 90	Male (single) = -1400 Female (single) = -1600

Table 8. continued...

First author, year	Location	Level of restriction / live weight change	Period of restriction	Difference in lamb birth weight relative to control (grams)
Kotsampasi, 2009	Greece	50% - ↓~4.5 kg	31 – 100	Male (twin) = -2400 Female (twin) = -1200 <i>Versus 100%PM</i> Male (single) = -1600 Male (twin) = -2600 Female (single) = +100 Female (twin) = +100
Aktas, 2013	Turkey	80%	100 – 142	<i>Versus 120%PM</i> Male (single) = 1400 Male (twin) = -2700 Female (single) = +400 Female (twin) = +400
Oliver, 2001	New Zealand	↓7 kg	105 – 115	Male (twin) = -1000 Female (single) = 0
Oliver, 2001	New Zealand	↓10 kg	105 – 125	Male (twin) = -1000 Female (single) = -1000
Hocking Edwards, 2011	Australia	Singles - ↓4 kg Twins - ↓7 kg	72 – 145	Single - Male + Females = -800 Twin - Male + Females = -3600
Goodchild, 1999	Syria	↑0.5 kg	126 – 150	Single - Male + Female = -800
Husted, 2007	Denmark	50% - 0 kg	105 – 147	Twin - Male + Female = -3600
Kelly, 1996	Australia	↓~8.8 kg	48 – 139	Male + Female (single) = -1700
Schinckel, 1961	Australia	NS	0 – 150	Male + Female (single) = -2800
Everitt, 1967	Australia	↓~7 kg	0 – 140	Male (single) = -5800 Female (single) = -4600
Everitt, 1967	Australia	↓~1 kg	90 – 140	Male (single) = -2100 Female (single) = -3300
Corner, 2008	New Zealand	↑6 kg until day 130	70 – 147	Male (twin) = -1600 Female (twin) = -1560
Corner, 2008	New Zealand	↑2.2 kg until day 130	108 – 147	Male (twin) = +140 Female (twin) = -2500
Kiani, 2011	Denmark	60% - ↓~5 kg	105 – 147	Twin - Male + Female = +430

Table 8. continued...

First author, year	First author, year	First author, year	First author, year	First author, year
Morris, 2004	New Zealand	↓~3 kg ^{CF}	64 – 147	<i>4 cm post-birth</i> Male+Female = -2750 (vs. 4 cm) Male+Female = -2440 (vs. 6 cm) Male+Female = -2840 (vs. 8 cm) <i>8cm post-birth</i> Male+Female = +300 (vs. 4 cm) Male+Female = -2570 (vs. 6 cm) Male+Female = -3850 (vs. 8 cm)
Nielsen, 2013	Denmark	50%	105 – 147	CONV Male + Female = -540 HCHF Male + Female = -1260
Sebert, 2011	England	60%	110 – 145	Twin - Male + Female = -3540
Sibbald, 1998	Scotland	70%	103 – 145	3 cm post-birth Female (twin) = -4100 6 cm post-birth Female (twin) = -600
Tygensen, 2007	Denmark	60%	105 – 147	GROWTH Male (twin) = -6300 MEAT Male (twin) = -5900

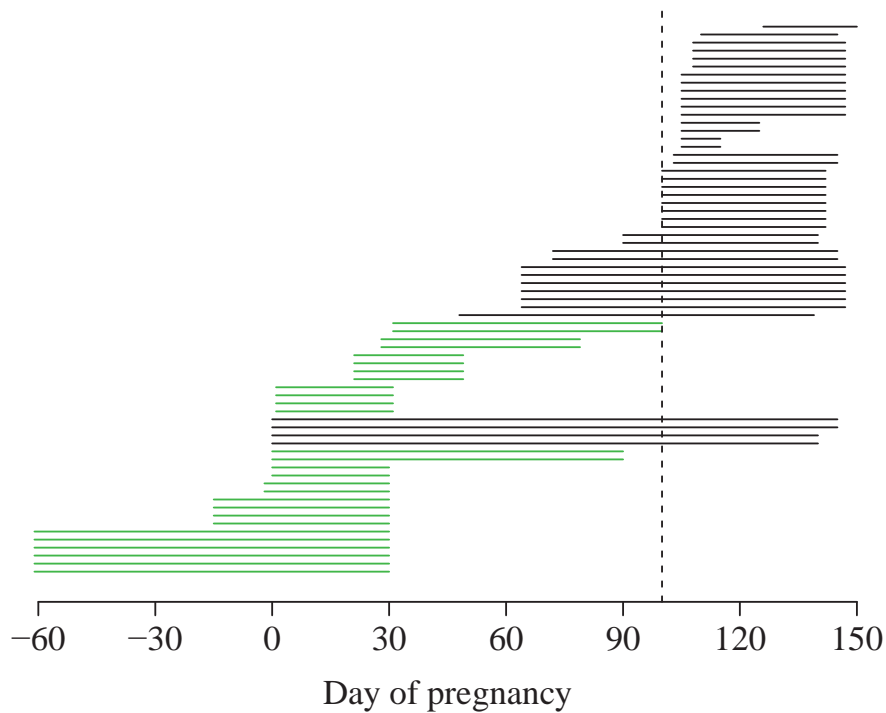


Figure 22. Line plot representing the undernutrition periods used across experiments. Green lines represent effects measured with nutritional manipulations ending before day 100 of pregnancy, whilst black lines represent effects measured with nutritional manipulations during late-pregnancy or nutritional manipulations that extended to late-pregnancy. Dotted line demarcates day 100 of pregnancy.

Whilst many variables were tested as possible sources of heterogeneity, two variables significantly influenced the weaning weight responses to maternal undernutrition across the selected studies: 1) the timing of undernutrition during pregnancy and 2) the length of the nutritional manipulations (Table 9). Including these two predictors in the meta-regression model explained almost 48% of the variation in data, reduced the variance at the experiment and dam breed level by 74% and 63%, respectively, but only decreased the residual variance by 9%. The decrease at the dam breed level variance suggested that dam breed is likely confounded with experimental design and was not investigated further.

However, the large decrease at the experiment level variance indicated substantial differences in weaning weight responses to undernutrition as pregnancy progressed.

Table 9. Results from the meta-analytic and meta-regression models in the undernutrition dataset. Estimates and highest posterior density intervals (95% HPD) in bold were considered statistically significant.

Description	Undernutrition dataset	
	Meta-analytic model	Meta-regression model
Fixed effects	β [95% HPD]	β [95% HPD]
Intercept	-0.45[-0.76 – -0.17]	-0.40[-0.63 – -0.21]
End day	–	-0.28 [-0.44 – -0.14]
Total days	–	-0.13 [-0.27 – -0.001]
Random effects	VC	VC
Experiment	0.147	0.038
Dam breed	0.088	0.033
Residual	0.045	0.041
PCV _[Experiment]	–	74%
PCV _[Dam breed]	–	63%
PCV _[Residual]	–	9%
I^2_{total}	66.50%	–
$R^2_{\text{LMM}(m)}$		47.79%
$R^2_{\text{LMM}(c)}$		81.02%
DIC	1.69	1.30

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

To further investigate these results, the timing of the nutritional manipulations was stratified into two periods: 1) nutritional manipulations ending before D100 of pregnancy and 2) nutritional manipulations during late-pregnancy (i.e. starting after D90 of pregnancy) or long-term nutritional manipulations extending into late-pregnancy. Individual analyses (e.g. meta-analysis and meta-regression) were performed within each subgroup of studies.

These subgroup analyses revealed that studies with nutritional manipulations ending before D100 of pregnancy (Period 1) showed less heterogeneity ($I^2_{\text{total}} = 39.48\%$) than studies with nutritional manipulations that included late-pregnancy ($I^2_{\text{total}} = 52.10\%$, Table 10). Overall, there was no evidence for the effects of nutrition during the first 100 days of pregnancy on lamb weaning weight ($\beta_{[\text{meta-analytic mean}]} = -0.08$, 95% HPD = -0.42 to 0.18). Although, the meta-regression analysis revealed a significant negative effect on lamb weaning weight ($\beta_{[\text{end day of manipulation}]} = -0.27$, 95% HPD = -0.48 to -0.08; Figure 23) as nutritional manipulations approached D100 (e.g. early-to-mid-pregnancy undernutrition). On the contrary, studies with nutritional manipulations that included the late-pregnancy period resulted in a significant decrease in lamb weaning weight relative to controls ($\beta_{[\text{meta-analytic mean}]} = -0.61$, 95% HPD = -0.86 to -0.38). The meta-regression analysis showed that lamb weaning weight was further decreased with increasing length of the undernutrition period ($\beta_{[\text{total days of manipulation}]} = -0.29$, 95% HPD = -0.48 to -0.11; Table 10, Figure 24).

Table 10. Summary of the statistical results of meta-analytic and meta-regression models in two subgroups from the undernutrition dataset. Period 1 refers to studies with nutritional manipulations ending within the first 100 days of pregnancy. Period 2 include studies undertaken in late-pregnancy or that extended to late-pregnancy. 95% highest posterior density (HPD) intervals excluding zero are considered statistically significant (in bold text).

Description	Models of the subgroup analyses			
	Period 1 subgroup		Period 2 subgroup	
	Meta-analytic model	Meta-regression model	Meta-analytic model	Additional model
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	-0.08[-0.42 – 0.18]	-0.07[-0.31 – 0.13]	-0.61 [-0.86 – -0.38]	-0.60 [-0.80 – -0.40]
End day	–	-0.27 [-0.48 – -0.08]	–	–
Total days	–	–	–	-0.29 [-0.50 – -0.11]
Random effects	VC	VC	VC	VC
Experiment	0.123	0.044	0.096	0.060
Residual	0.015	0.012	0.069	0.061
PCV _[Experiment]	–	64%	–	38%
PCV _[Residual]	–	20%	–	12%
I^2_{total}	39.48%	–	52.10%	–
$R^2_{\text{LMM}(m)}$	–	55.93%	–	41.37%
$R^2_{\text{LMM}(c)}$	–	90.42%	–	70.40%
DIC	-58.19	-60.40	18.79	16.02

VC, variance components; PCV, proportion change in variance; DIC, deviance information criterion

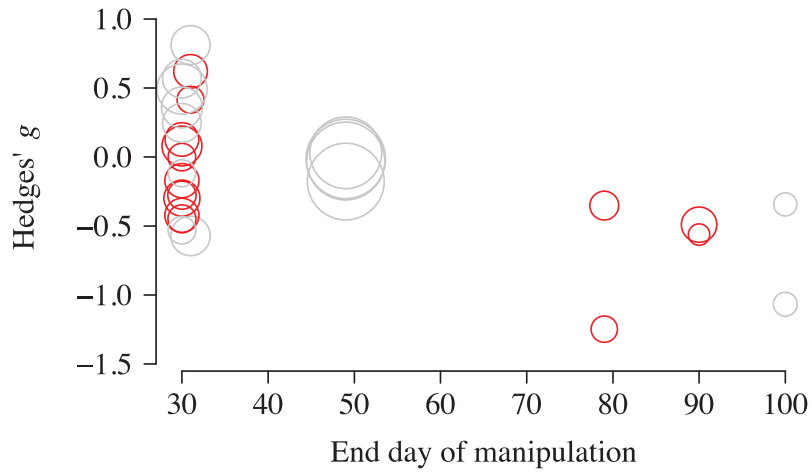


Figure 23. Bubble plot of effect-sizes in studies with nutritional manipulations ending before day 100 of pregnancy. Red and grey bubbles represent studies undertaken in singletons and twins, respectively. Differences in bubble circumference represent the precision (1/SE) of the study.

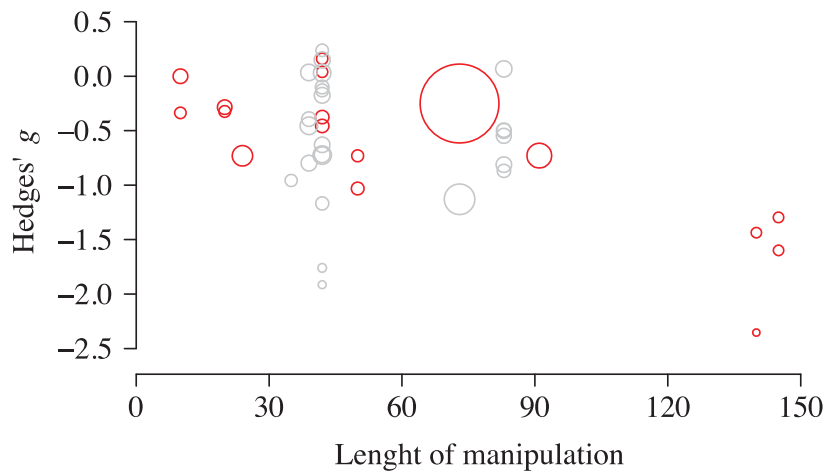


Figure 24. Bubble plot of effect-sizes against the length of nutritional manipulations of studies undertaken in late-pregnancy or that extended into late-pregnancy. Red and grey bubbles represent studies undertaken in singletons and twins, respectively. Differences in bubble circumference represent the precision (1/SE) of the study.

4.4.2.2 Overnutrition

Only six studies were available for the overnutrition meta-analysis, from which 24 ES were extracted. A graphic representation of the nutritional manipulations within this dataset is presented in Figure 25. Given the limited number of studies in this dataset, analyses were narrowed to only a meta-analytic model presenting the overall effect across studies. The overall effect of overnutrition on lamb weaning weight is summarized graphically in Figure 26. Results across studies showed only small heterogeneity ($I^2_{\text{total}} = 33.53\%$) and indicated that feeding ewes above their requirements for pregnancy significantly increased lamb weaning weights relative to controls ($\beta_{[\text{meta-analytic mean}]} = 0.25$, 95% HPD = 0.01 to 0.45).

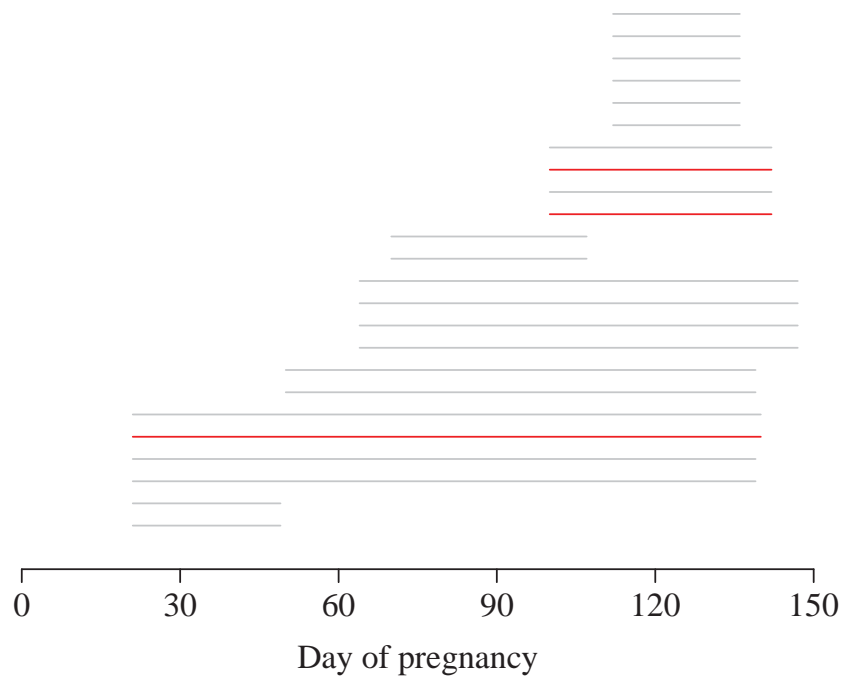


Figure 25. Line plot representing the overnutrition periods used across experiments. Red and grey lines represent studies undertaken in singletons and twins, respectively.

First author / year

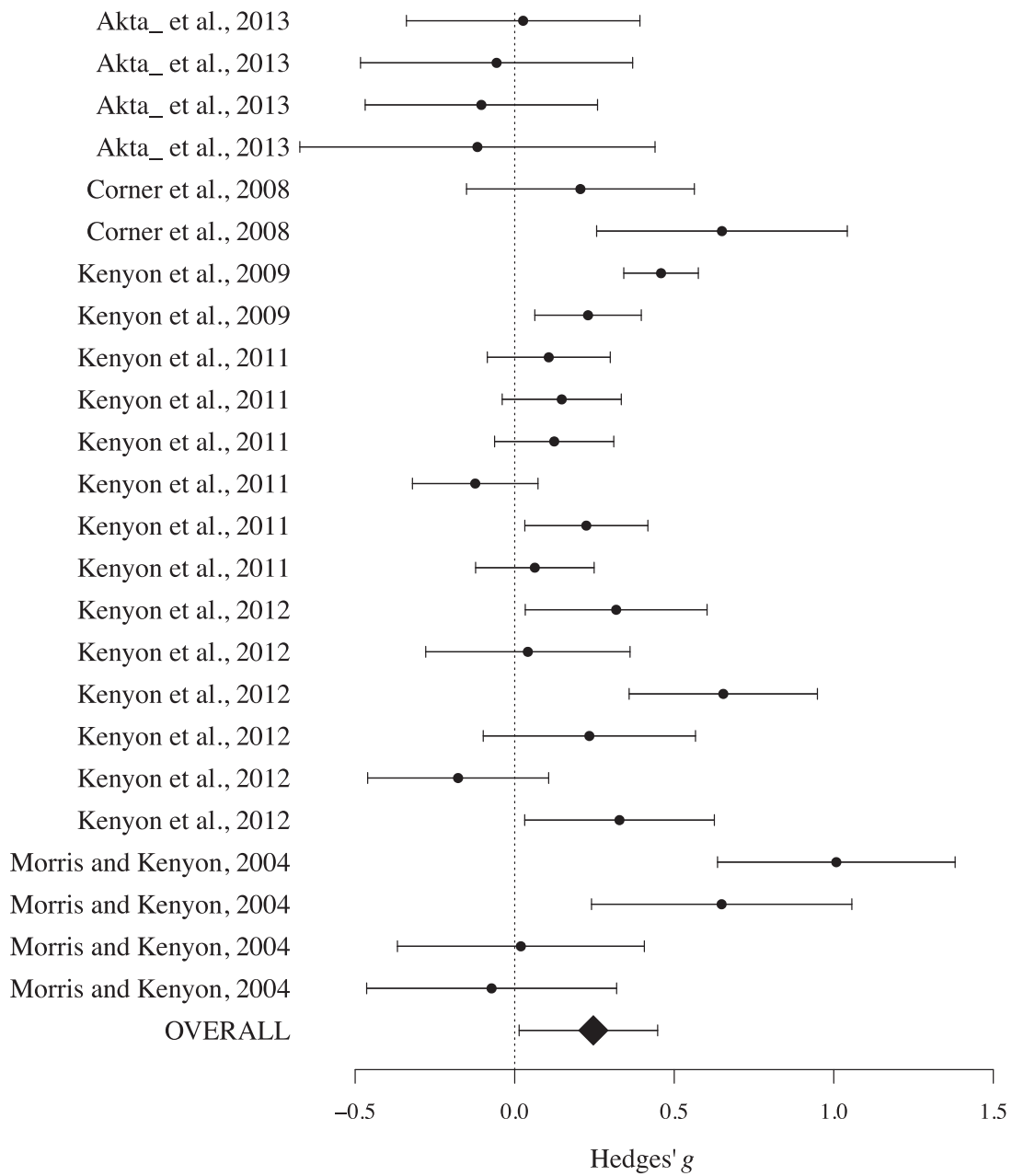


Figure 26. Forest plot of effect-sizes (ES) extracted from the overnutrition studies and the overall effect estimated using random-effects meta-analysis. The raw ES for each study is represented by a dot (●) their estimated standard errors (SE of Hedges' g). The overall effect (◆) is the posterior mean and 95% highest posterior density (HPD) interval from the meta-analytic model.

4.4.3 Publication bias and sensitivity analysis

In the undernutrition dataset, a significant intercept for the Egger's regression test ($\beta_{[\text{Intercept}]}$ = -0.92, 95% HPD = -1.38 to -0.41) and the associated observed asymmetry in the funnel plots (Figure 27a and Figure 27b) illustrate a bias towards small studies showing a negative effect on lamb weaning weight and a lack of studies showing potentially positive effect as a consequence of undernutrition during pregnancy. On the contrary, the non-significant intercept of Egger's approach suggested no evidence of publication bias in the overnutrition dataset ($\beta_{[\text{Intercept}]}$ = -0.29, 95% HPD = -1.47 to 0.74; Figure 27c).

Using the trim-and-fill test to correct for the potential publication bias in the undernutrition dataset revealed four studies missing from the right hand side of the funnel plot. However, further exploration of this potential publication bias was performed since it was evident from Figure 27a and Figure 27b that there were clear differences in estimated effects between studies that did not include late-pregnancy (green dots; Period 1) and those that did (black dots; Period 2). Thus, separate Egger regressions were performed for each subgroup. This approach revealed that the publication bias seen in the overall undernutrition dataset was largely due to experiments with nutritional manipulation that included late-pregnancy ($\beta_{[\text{Intercept} - \text{Period 1}]}$ = -0.59, 95% HPD = -1.38 to 0.30; $\beta_{[\text{Intercept} - \text{Period 2}]}$ = -1.18, 95% HPD = -1.77 to -0.57). This would suggest a lack of small late-pregnancy undernutrition studies potentially showing large positive effects on lamb weaning weight. However, given the moderate variation among effect-sizes in this subgroup, and the potential effects of late-pregnancy undernutrition on fetal growth, birth weight and on the ewe's milk production, it is possible that heterogeneity may be responsible for the observed funnel plot asymmetry rather than true publication bias.

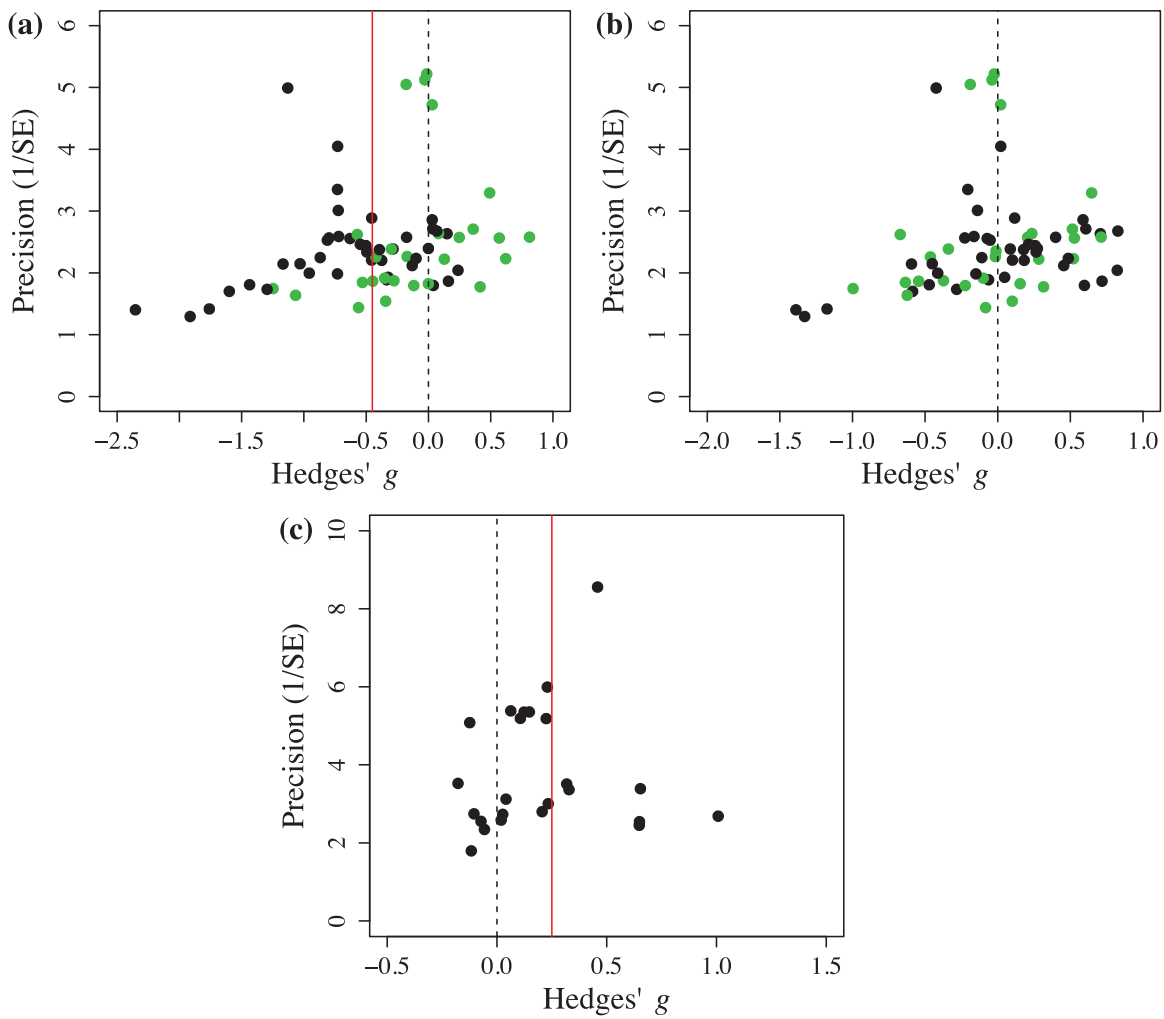


Figure 27. Funnel plots of raw (a and c) and the residuals and sampling error effects from meta-regression models (b) in the undernutrition (a and b) and overnutrition (c only) datasets. Overall posterior (meta-analytic) means are shown as red solid lines and zero effect is shown as dashed lines. Observations in green and black in the undernutrition funnel plots depict studies undertaken in Period 1 (nutritional manipulations during the first 100 days of pregnancy) and Period 2 (nutritional manipulations including late-pregnancy).

4.5 Discussion

In summary, this meta-analysis represents the first evidence-based study to quantitatively combine studies examining the effect of maternal pregnancy nutrition on lamb weaning weight. In the previous meta-analyses (Chapter 2 and 3) it was established that poor nutrition of the pregnant ewe, especially during late-pregnancy, affects the development of the fetus and its subsequent weight at birth. The present study extends this evidence showing that when nutrition post-lambing is non-limiting (i.e. meeting or exceeding the ewe's nutritional requirements), the negative effect of poor nutrition during pregnancy remained until weaning. Both, the timing and length of undernutrition played a significant role in determining the magnitude of responses across studies. Undoubtedly there is a cumulative effect of pregnancy and lactation nutrition on lamb weaning weight (Caton and Hess, 2010), although from the analysis undertaken in the present study it is not possible to determine whether the decrease in weaning weight detected was a consequence of lambs being born lighter, the result of potential effects on ewe's milk production or both. In addition, this meta-analysis revealed that supplying the ewe with nutrients beyond those required for meeting pregnancy requirements could increase lamb weaning weights. Although, there has been a small number of experiments so far and thus questions remain as to what stage of pregnancy and what length of above PM feeding is necessary to instigate such increase in weaning weight.

The results from this meta-analysis suggested that undernutrition of the pregnant ewe in early-pregnancy had no impact on lamb weaning weights. Even when negative effects were observed (i.e. with nutritional manipulations extending to day 100), the magnitude of these effects was relatively small compared to the effect of late-pregnancy and long-term

undernutrition, which supports previous narrative reviews (Greenwood and Thompson, 2007; Kenyon and Blair, 2014) and systematic reviews (Rooke et al. 2015). This finding is important for two reasons: first, it confirms our hypothesis and previous finding from large-scale experiments (Coop and Clark, 1969; Thompson et al. 2011) and comprehensive reviews (Greenwood and Thompson, 2010; Kenyon and Blair, 2014; Bell and Greenwood, 2016) that potential effects on weaning weight as a result of undernutrition during the first 100 days of pregnancy can be minimized by appropriate nutrition in later stages. Second, it also suggests that offspring effects as a consequence of severe or prolonged mid-pregnancy maternal undernutrition are not fully compensated for by weaning time, despite appropriate nutrition in late-pregnancy and post-lambing. Combined, the evidence presented here indicated that lamb weaning weights are at optimum when nutrient requirements are met during the first 100 days of pregnancy. That means, farmers need to maintain ewes' live weight during the first month of pregnancy, expect an increase in ewe live weight until day 90 to 100 of pregnancy, similar to that of the expected conceptus mass, whilst maintaining the ewe's mating body condition. Though, from a lamb's weaning weight perspective, if farmers envision a potential feed shortage during this period, ewes can be allowed some live weight loss without affecting lamb performance to weaning. Additional factors need to be considered when providing feeding guidelines during this period, because undernutrition has been shown to influence embryo survival (Rhind et al. 1985, 1989), placental mass (Heasman et al. 1998; McCrabb et al. 1992), lamb survival (Thompson et al. 2011), ewe live weight and BCS in pregnancy and post-weaning (Doney et al. 1981; Smeaton et al. 1983). All of these factors have the potential to compromise productivity and ultimately farm profitability.

This meta-analysis also showed that undernutrition during late pregnancy could result in a decrease in weaning weight of between 9% and 18% when compared to lambs born to adequately fed dams. Longer periods of undernutrition (that is, if undernutrition started prior to late-pregnancy, which could potentially affect their body reserves prior to day 100 of pregnancy) can further negatively affect lamb weaning weights. Therefore, farmers need to devise appropriate feeding strategies during late pregnancy. These results, combined with the previous meta-analyses (Chapter 2 and 3) and the existing knowledge (Greenwood and Thompson, 2007; Caton and Hess, 2010; Greenwood et al. 2010; Kenyon and Blair, 2014; Bell and Greenwood, 2016; Rooke et al. 2015) indicate that ewes in poor nutritional status prior to day 100 of pregnancy or those carrying multiples should be targeted in late pregnancy if feeding conditions don't allow all ewes to be fed adequately.

In this study, increasing feeding levels beyond those needed for pregnancy maintenance was associated with up to a 9% increase in lamb weaning weight, although the lower bound of the estimated 95% HPD interval suggests that, in some circumstances, feeding adult ewes above their requirements for pregnancy offers very little practical advantage to increase lamb weaning weights. From the present study, and despite the significance of these results, it is not possible to determine a specific time in pregnancy or a particular length of overfeeding that is able to generate such effects and therefore results remain inconclusive. Therefore, additional research is required. Further, two practical components require consideration: first, extended periods of above pregnancy maintenance feeding may not be cost-effective considering the magnitude of the potential effect and the cost of the extra feed. Secondly, overfeeding ewes in early- and mid-pregnancy can promote excessive

LW and BCS gains. Fat ewes can suffer from limited appetite during late-pregnancy (Gordon and Tribe, 1951, Holst et al. 1986), which can have negative impacts.

4.6 Conclusions

Failing to provide ewes with the minimum requirements for late-pregnancy resulted in decreased weaning weights, with more substantial effect when ewes have suffered extended periods of undernutrition. On the contrary, undernutrition during the first 100 days of pregnancy had more variable effects, but on average, this meta-analysis suggests that there are no major consequences to the lambs in regards to their weaning weight. Further, results suggest that increasing lamb weaning weights by feeding ewes above their pregnancy maintenance requirements may be possible in some circumstances, but potential effects and their practical applications are yet to be identified, as literature is still scarce in this area. Therefore, these results coupled with the findings in Chapter 2 and 3 indicate that farmers need to devise managerial practices that focus on meeting the ewe's requirements at each stage of pregnancy. If conflict between feed demand and availability does not allow all ewes to be fully fed to their PM requirements, ewes can be allowed some live weight loss during the first 100 days of pregnancy without critically affecting lamb performance to weaning. During late-pregnancy, however, prioritising the feeding of ewes in poor nutritional status prior to day 100 of pregnancy and those carrying multiples is essential to achieve optimum lamb live weights for birth to weaning. Given the current magnitude of the estimated effect, feeding ewes above their PM requirements offer no considerable advantage to increase weaning weight relative to PM feeding. Future research is needed to corroborate the small and perhaps unmeasurable effects of early and mid-pregnancy undernutrition at the farm level (i.e. via large-scale experiments). Further studies are also

required to determine if an interaction exist between the timing and length of above pregnancy maintenance feeding that can result in a sufficient increase in lamb weaning weights so that productivity can be increased.

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4.8 Supplementary material for Chapter 4

4.8.1 Supplementary tables

Table S4.1 Main characteristics of the studies included in the undernutrition meta-analysis. Period 1 refers to studies with nutritional manipulations ending within the first 100 days of pregnancy. Period 2 refers to studies undertaken in late-pregnancy or that extended to late-pregnancy (long-term undernutrition).

Description	Period of analysis (days; where 0 is conception and 150 is approximate pregnancy term)	
	Period 1	Period 2
No. of effect sizes per subgroup *	28	41
Start of restriction (day post-conception)		
Mean (\pm SD [†])	-8 \pm 31	85 \pm 33
Range	-61 – 31	0 – 126
End of restriction (days post-conception)		
Mean (\pm SD)	46 \pm 25	142 \pm 8
Range	30 – 100	115 – 150
Duration of restriction (days)		
Mean (\pm SD)	54 \pm 26	57 \pm 35
Range	28 – 91	10 – 145

* Refers to studies ending within each particular stage of pregnancy.

[†] SD, standard deviation

4.8.2 Supplementary references - list of excluded studies

Adolescent sheep

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Study design not in accordance with Chapter hypothesis

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Chapter 5: Feeding adult multiparous ewes
above their pregnancy maintenance
requirements does not increase lamb birth
weight or their growth to weaning

5.1 Abstract

Few studies have considered the effects of feeding mature ewes above their theoretical requirements for pregnancy on the performance of the resulting lambs. Previous meta-analyses showed that little is known about the interaction between the stage of pregnancy and length of above pregnancy maintenance (PM) feeding and how this may affect the growth of lambs from birth to weaning. The present study aimed to examine this interaction by providing mixed-aged, twin-bearing Romney ewes one of six pastoral feeding treatments: PM-feeding throughout pregnancy (Control), *ad-libitum* (AL) feeding from day 0 (P0) of pregnancy to P50 (AL050), AL feeding from P50 to P100 (AL50-100), AL feeding from P100 to P140 (AL100-140), AL feeding from P0 to P100 (AL0-100) and AL feeding throughout pregnancy (AL0-140). Outside the AL feeding periods, ewes in those treatments were given pasture allowance similar to the control group. Ewe live weight (LW) and body condition score (BCS) in pregnancy and lactation and lamb live weight from birth to weaning were recorded. *Ad-libitum* feeding increased ($p < 0.05$) ewe LW and BCS in all treatments compared to Control on at least one occasion in pregnancy, but did not increase lamb birth weight ($p > 0.05$) or weaning weight ($p > 0.05$). However, gestation length was shorter ($p < 0.05$) in the AL0-140 treatment ewes than all other groups and lambs born in the AL100-140 treatment had lower ($p < 0.05$) survival percentage than those born in the AL50-100 treatment. Given the absence of effects on lamb birth weight and weaning weight, and the potential negative impact of AL feeding during late-pregnancy on lamb survival, AL feeding of pregnant ewes is not justified as a managerial tool to increase twin-lamb birth weights and weaning weights.

Key words: *ad-libitum*, maternal nutrition, lamb birth weight, weaning weight.

5.2 Introduction

The nutritional management of the pregnant ewe, especially during late-pregnancy, is a major factor influencing fetal growth and ultimately lamb birth weight and survival (Mellor, 1983; Kelly and Newnham, 1990; Gootwine, 2013; Oldham et al. 2011). Ewe feed requirements in early pregnancy (day 1 to 30) are equivalent to the maintenance requirements of non-pregnant ewes (NRC, 1985). During this period, absolute growth rates of the developing embryo are small although, ‘relative’ growth rates (i.e. percentage per day) are high (Koong et al. 1975; Robinson, 1977; Reynolds and Redmer, 1995). Early-pregnancy is also a critical time for the differentiation and development of fetal organs and the placenta (Grazul-Bistka et al. 2013). During mid-pregnancy (days 31 to 90), ewe feed requirements are only slightly above maintenance (NRC, 1985), and yet, the placenta reaches its maximum weight during this period (Ehrhardt and Bell, 1995). In contrast, during late-pregnancy (day 91 to term) the nutritional requirements of the ewe increase significantly as a consequence of approximately 85% of fetal growth occurring in this period (Robinson, 1977).

In the previous three chapters, an extensive review of nutritional studies in adult sheep was undertaken using both a systematic review and meta-analytic approach. The results indicate that only few studies that have considered the effects of feeding mature ewes above their requirements for pregnancy on fetal growth and lamb live weight from birth to weaning, especially at each stage of pregnancy. Previous narrative (Caton and Hess, 2010; Kenyon and Blair, 2014; Bell and Greenwood, 2016), systematic reviews (Rooke et al. 2015) suggested that feeding ewes above their pregnancy maintenance (PM) requirements have a limited impact on the weight of lambs from birth to weaning. Yet, the meta-analyses

presented in this thesis showed that feeding ewes above their requirements for pregnancy may have positive effects on lamb birth weight and weaning weight. Although, it was also found that the paucity of information that is available is inconsistent as studies differ considerably in design, which have led to a wide variation in study results. Therefore, it is still unknown whether there is an interaction between the stage of pregnancy and the length of above pregnancy maintenance feeding that could explain such variation in results. This limited of information prevented clear conclusion to be drawn from the available literature. The present study was therefore designed to add to the understanding of this interaction by studying the effect of short and long periods of *ad-libitum* (AL) feeding of twin-bearing ewes at various stages of pregnancy and its effects on lamb birth weight and their weight during the pre-weaning period. It was hypothesised that AL feeding would increase lamb birth weight regardless of the stage of pregnancy. It was further hypothesised that this positive effect on lamb birth weight would be increased with increasing length of AL feeding. Further, it was hypothesised that AL feeding would result in greater lamb weaning weights when compared to pregnancy maintenance feeding.

5.3 Materials and Methods

The ARRIVE guidelines (Kilkenny et al. 2010) have been developed to improve the design, analysis and reporting of research involving animals, especially those with human applications. The present study therefore used the ARRIVE guidelines, were applicable, to address the reporting quality issues that currently exist in animal science and that have been discussed in previous chapters (see 5.8 Supplementary Material: ARRIVE guidelines checklist).

5.3.1 Experimental design

The present study was conducted at Massey University's Keeble Research Farm, 5 km south of Palmerston North, New Zealand (Latitude: 40°23'34" South, Longitude: 175°36'09" East; 50-m altitude) during the period from March to December 2015. All handling procedures in the present experiment were conducted with the approval of Massey University's Animal Ethics Committee (Animal Ethics form code 15/06).

This study used 200 twin-bearing, mixed aged (3 to 6 years) Romney ewes that were randomly distributed into one of six nutritional treatments post artificial insemination (AI), as follow:

- Control (C): Pregnancy maintenance (PM) feeding throughout pregnancy from AI to P140.
- Treatment 1 (AL0-50): 50 days of *ad-libitum* feeding from AI to day 50 of pregnancy (P50).
- Treatment 2 (AL50-100): 50 days of AL feeding from P51 to P100.
- Treatment 3 (AL100-140): 40 days of AL feeding from P101 to P140.
- Treatment 4 (AL0-100): 100 days of AL feeding from AI to P100.
- Treatment 5 (AL0-140): Ad-libitum feeding throughout pregnancy from AI to P140.

In all AL treatments, outside of their stated AL feeding periods, ewes received the same pasture allowance as control ewes (Figure 28). In order to achieve the six selected treatments, Cohen's guidelines for power calculation (Cohen, 1988) were used to estimate

the ideal sample size for this study with 800 mixed-age Romney ewes (sourced from two commercial farms) available. The assumptions regarding the animals in the present study were as follow:

1. 613 ewes expected to conceive.
2. 50/50 ratio of singleton and twin bearing ewes.
3. 80% surviving twin births.
4. Any potential feeding strategy that can successfully be applied on-farm needs to be sizeable enough to affect the productivity and profitability of sheep farmers. An increase in 500 grams in twin lambs may have the potential to positively affect both the animal's survival and productivity, as well as the farmer's profitability if this advantage is carried through to later stages in life.
5. Means for all treatments would span a range of 68% of the within-population standard deviation of 0.74 (taken from a previous trial; Kenyon et al. 2011).
6. Medium variability between groups and all means equally spaced along a value of $d = 0.68$.

Twenty-five days (P-25) prior to AI, ewes were managed as a group and offered herbage at a minimum post-grazing herbage mass of 1200 kg DM/ha. On each of P-16 and P-15, 400 randomly selected ewes were synchronised via insertion of progesterone-controlled internal drug-release devices (CIDR, 0.3 g progesterone, Pharmacia & Upjohn, Auckland, New Zealand) to induce oestrus. On P-2, ewes were weighed and CIDRs were removed from ewes that had had them inserted on P-16, with the remainder removed the following day (P-1).

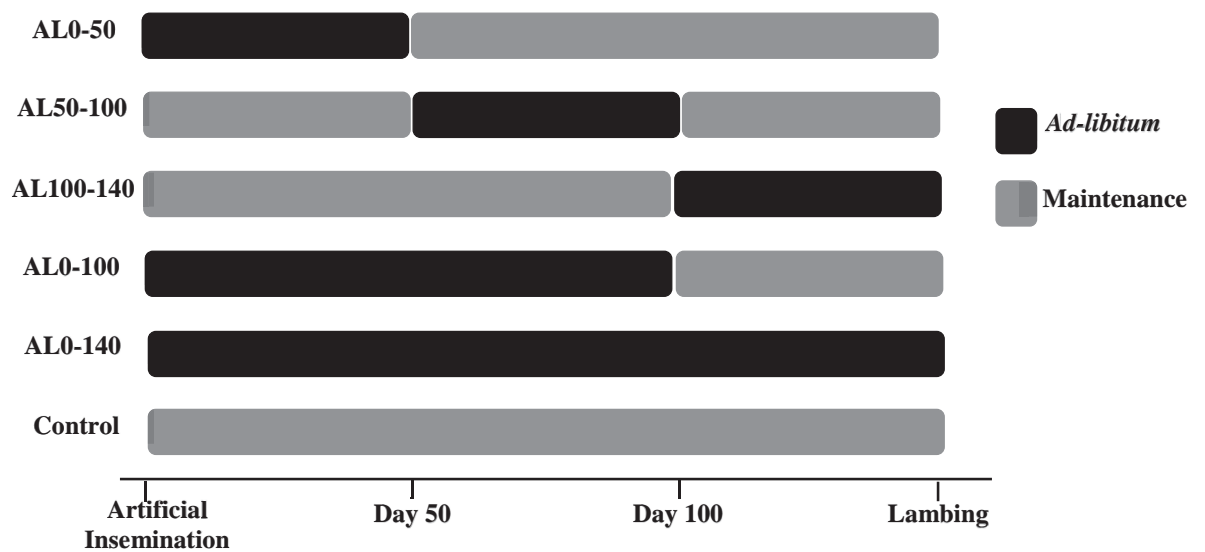


Figure 28. Schematic representation of the six nutritional treatments used in this study. AL0-50 = maternal *ad-libitum* (AL) feeding from artificial insemination (AI) to P50; AL50-100 = maternal AL feeding from P50 to P100; AL100-140 = maternal AL feeding from P100 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI to P140. Outside the aforementioned AL feeding periods, ewes were offered herbage at pregnancy maintenance levels.

Artificial insemination of ewes whose CIDRs were removed on P-16 and P-15 was performed via intra-uterine laparoscopy and took place over two days (P0 and P1, respectively). Ewes were removed from pasture at 1600h on the previous day to AI and held overnight in woolshed yards, with no water allowed during this period. On each AI day, simple randomization was used to allocate ewes to fresh semen from one of four Romney rams and two levels of feeding: PM and AL until P50 (mean and standard deviation of ewes at each level of feeding was 68.2 ± 7.0 and 68.1 ± 6.5 , respectively). Artificial insemination commenced each day at 0800h and finished by 1300h on the same

day. Each ewe was tranquilised with i.m. injection of acetyl chlorpromazine (approx. 1ml of 10 mg/mL ACP) and placed on mobile laparoscopy cradles. Belly wool was removed using electric clippers and skin surface washed and cleaned with antiseptic solution. Local anaesthetic (lignocaine hydrochloride, 20 mg/mL; approx. 4mL) was infused in each side of the ventral midline anterior to the mammary gland. Entry to the abdominal cavity for the laparoscope followed puncture using a trochar and cannula (usually right side of midline), whilst insertion of the manipulating probe (on the left side of midline) was made with a pointed scalpel. Inflation of the abdominal cavity with carbon dioxide (from a cylinder) or air (from a foot pump) was performed using a bevelled needle inserted through the abdominal wall. Following AI, the wounds were treated with aureomycin antibiotic powder and the ewe was injected i.m. with procaine penicillin (~ 20mg/mL). Ewes were then removed from the laparoscopy cradle and allowed to walk in an adjacent paddock with access to water and pasture. All ewes were observed for at least one-hour post AI to ensure adequate recovery from sedation.

In this study, the term “pregnancy maintenance” is defined as the amount of herbage required to maintain ewe net live weight throughout pregnancy, whilst allowing for adequate growth of the fetus at each individual stage of pregnancy (as indicated by Nicol and Brookes, 2007). Pregnancy maintenance feeding was achieved by using a combination of target pre- and post-herbage masses, size of grazing area, ewe live weight and body condition scores (BCS). *Ad-libitum* is defined as unrestricted access to ryegrass/white clover swards ensuring that post-grazing masses did not go below 1200 kg DM/ha. Previously, Morris and Kenyon (2004) indicated that ewe intakes on ryegrass-white clover swards are unrestricted above 1200 kg DM/ha. Eight crayon-harnessed entire Romney rams

were introduced on P6 and remained with the ewes until P26. At P26 all ewes marked on the rump by the rams, an indication of rebreeding, were removed from the study (n = 406). At P47, all ewes were pregnancy scanned by transabdominal ultrasonography and all non-pregnant (n = 37), singleton- (n = 124) and triplet-bearing ewes (n = 33) were then removed from the study.

At P50, the remaining twin-bearing ewes from the PM (n = 102) and AL (n = 98) treatments were then randomly allocated into one of the six nutritional treatments depicted in Figure 28. For the remaining of pregnancy, at any one time, ewes were managed in just two groups (PM or AL), depending on their individual treatments. Thus, from P50 to P100, ewes in AL0-50 (n = 32), AL100-140 (n = 34) and C (n = 34) were managed together and fed to meet the PM requirements for mid-pregnancy on the control treatment, whilst ewes in AL50-100 (n = 34), AL0-100 (n = 33) and AL0-140 (n = 33) were managed together with unrestricted access to pasture. On P100, nutritional treatments were again rearranged such that ewes in AL0-50, AL50-100, AL0-100 and C were fed to meet the PM requirements for late-pregnancy, whilst AL100-140 and AL0-140 ewes were offered unrestricted access to pasture.

On P140, nutritional treatments were completed and ewes were randomly allocated to lambing paddocks at a rate of 14.3 ewes/ha, with an average herbage pre-grazing mass of 1593 ± 12 (s.e.) kg DM/ha. Ewes remained in their lambing paddocks until 11 days after the mid-point of the lambing period (L0; lambing started on P140 and lasted 13 days). Thereafter, until L49 ewes and their lambs were managed under commercial grazing conditions in four randomly allocated groups (number of ewes in each group were 45, 50,

44, 49), which contained individuals from each of the six nutritional treatments. Then on L49, ewes and their lambs were managed in two groups (94 ewes in each group) until weaning on L97. During the lactation period, animals were managed via pasture rotation to ensure herbage covers remained above 1200 kg DM/ha.

5.3.2 Pasture measurements

Nutritional treatments were monitored every day by measuring herbage masses via 150 readings of a rising-plate meter per paddock grazed (Ashgrove Pastoral Products, Hamilton, New Zealand). Targeted pre- and post-grazing herbage masses, size of the grazing area and ewe live weights were used to determine when ewes needed to be moved to ensure they achieved their target nutritional treatment. A standard calibration was used to transform the average plate meter readings into herbage mass using the following formula (Hodgson et al. 1999):

$$\text{Pasture mass (kg DM/ha)} = (158 \times \text{average plate meter reading}) + 200$$

A representative sample of the pasture that ewes were consuming was collected fortnightly via a grab sample during pregnancy and monthly during lactation. These pasture grab samples were analysed for levels of neutral and acid detergent fibre (NDF and ADF, respectively), metabolisable energy (ME) and starch and soluble sugars (SSS) by near infrared reflectance (NIR, Corson et al. 1999).

5.3.3 Animal measurements

Live weight measurements for all ewes were taken within 2 hours of being removed from pasture and were recorded on 14 occasions: prior to AI (P-2) and at P5, P14, P25, P36, P50,

P53, P67, P90, P100, P102, P109, P124 and P140. A single experienced operator determined the body condition scores (BSC, Kenyon et al. 2014, scale 0 to 5, including half units) of ewes on all weighing days, except on P53 and P102 when BCS was not recorded. During the lambing period, ewes were monitored twice daily between 8 and 11 am and again between 2 and 5 pm. Lamb measurements were taken within 12 hours of birth regardless of whether the lamb was dead or alive at each monitoring time. Lambs that appeared to be recently born at each monitoring time were left undisturbed to enable the ewe and lamb to bond and measurements were taken in the subsequent monitoring period. Lamb measurements recorded near birth included: mother identification, individual lamb identification (ID), sex of the lamb, birth weight and body measurements (crown-rump (CRL), chest circumference (CC), foreleg (FL) and rear leg (HL) lengths). Ewe live weights and body condition scores and further lamb live weights were recorded in the lactation period on L20, L48, L64, L82 and L97.

5.3.4 Statistical analysis

5.3.4.1 *Animal numbers*

Complete ewe and lamb data until lambing were available for 185 twin-bearing ewes (n = 29, 32, 32, 31, 31 and 33 for AL0-50, AL50-100, AL100-140, AL0-100, AL0-140 and control nutritional treatments, respectively) and their 370 twin-born lambs. Incomplete ewe and lamb data (i.e. data from incomplete twin sets) were collected from two ewes in AL0-100 and one ewe in AL0-50 in which the one live lamb was accompanied by a mummified sibling from which data were not obtained. Data from 12 ewes were removed because they corresponded to three ewes that died throughout the course of the experiment in AL50-100, AL0-100 and AL0-140, four ewes that gave birth to singleton lambs in AL50-100, AL0-

100, AL0-140 and C, one ewe giving birth to triplets and one abortion both in AL0-50 treatment and three ewes that failed to lamb from AL0-50 (1 ewe) and AL100-140 (2 ewes). Post-lambing, data from three additional ewes and their lambs (from AL0-50, AL0-100 and C) were unavailable due to either ill health or death of the ewe.

5.3.4.2 Data analyses

All statistical analyses were conducted using the Statistical Analysis System software version 9.4 (SAS Institute Inc., Cary NC, USA). The LW and BCS of ewes during pregnancy were analysed using repeated measurement analysis as implemented in the MIXED procedure with a model that included the fixed effects of nutritional treatment, time of measurement and their interaction. Ewe source (i.e. the commercial farm from which the ewes were obtained) was used as a random effect. Using Akaike's information criterion, an 'unstructured error' structure was determined as the most appropriate residual covariance structure for repeated measures over time within ewes. Least square means for ewe LW and their standard errors were obtained for each nutritional treatment for P-15/P-16, P-2, P5, P14, P25, P36, P50, P53, P67, P90, P100, P102, P109, P124 and P140. Least squared means were obtained for BCS at P-2, P50, P100 and P140.

Gestation length for each ewe was calculated as the differences between the lambing and AI date. The difference in gestation length between treatments was then tested using a linear mixed model that included the fixed effect of nutritional treatment and ewe farm source and ram as random effects. The probability that ewes within nutritional treatments would lamb before day 149 of pregnancy, hereafter referred as lambing rate (1 = lambed, 0 = not lambed) was analysed in a model that included the nutritional treatment as a fixed effect

and ewe farm source, AI date and ram as random effects. This analysis was performed using PROC GLIMMIX with a binomial distribution and logit transformation of the data.

Differences in average lamb birth weight and other morphological measurements at birth were analysed using two models. Both models included maternal nutritional treatment, sex of lamb and their two-way interaction as fixed effects and ewe farm source, ewe within farm source and ram as random effects. In the second model, gestation length was also included as a covariate and was fitted as the deviation from the median gestation length across all ewes (GLX) and was individually estimated as follow:

$$\text{GLX} = \text{gestation length} - 149$$

Post-lambing, ewe LW and BCS data at each time point was analysed using mixed models that included ewe farm source and post-lambing grazing group as random effects, pregnancy nutritional treatment, and ewe rearing rank (1/2 or 2/2) as fixed effects and lambing date as a covariate (fitted as the deviation from median lambing date). Similarly, individual lamb LW data post-birth were analysed with models that included ewe farm source, ewe within farm source, post-lambing grazing group and ram as random effects; maternal nutritional treatment during pregnancy, sex of lamb, their two-way interaction and lamb rearing rank were used as fixed effects with lamb age at each measurement as a covariate. Lamb age was fitted as the deviation from the median lamb age at each measurement time, which at L20, L48, L62, L82 and L97 were 18, 46, 62, 80 and 95 days, respectively.

For each ewe, total litter birth and weaning weight were analysed using a mixed model that included ewe farm source and ram as random effects and ewe nutritional treatment during pregnancy as fixed effect. For incomplete twin sets at weaning (i.e. one lamb not present at weaning) a value of 0 kg was given to calculate total litter weaning weight. For total litter weight at birth, the deviation from the median gestation length was fitted as a covariate, whereas for total litter weight at weaning (L97), the deviation from the median lamb age at weaning was used as a covariate. Lamb survival to P97 was analysed as a binomial trait (1 = alive, 0 = dead) using PROC GLIMMIX with a logit transformation of the data. The mixed model for lamb survival included the ewe nutritional treatment, sex of lamb and their interaction as a fixed effects and ewe within farm source and ram as random effects.

Differences in pre- and post-grazing herbage masses across nutritional levels and at each stage of pregnancy were analysed using the MIXED procedure with a model that included nutritional level (PM or AL), stage of pregnancy and their two-way interaction as fixed effects.

5.4 Results

5.4.1 Herbage mass

At all periods, the AL pre- and post-grazing herbage masses were greater ($p < 0.001$) than those of the PM group (Table 11). There were no differences ($p > 0.05$) in any of the quality herbage measures between PM and AL groups (Table 12).

Table 11. Pre- and post-grazing herbage masses of pregnancy maintenance (PM) and ad-libitum (AL) herbage allowances (least squares means \pm SEM) offered to ewes during early-pregnancy (pregnancy day 1 (P1) – P50), mid-pregnancy (P51-P100) and late-pregnancy (P101-140).

Stage of pregnancy	Pre-grazing herbage mass (kg DM/ha)		Post-grazing herbage mass (kg DM/ha)	
	PM	AL	PM	AL
Early-pregnancy P1 – P50	926 \pm 53 ^a	2420 \pm 63 ^b	656 \pm 20 ^a	1544 \pm 23 ^b
Mid-pregnancy P51 – P100	732 \pm 29 ^c	1781 \pm 44 ^d	540 \pm 11 ^c	1315 \pm 16 ^d
Late-pregnancy P101 – P140	1077 \pm 35 ^e	1477 \pm 47 ^f	572 \pm 14 ^e	1257 \pm 17 ^f

SEM, standard error of the mean.

^{abcdef} Different superscripts within pre- and post-grazing herbage masses and between levels of feeding (PM vs. AL) at each stage of pregnancy differ significantly ($p < 0.001$).

Table 12. Chemical composition and metabolizable energy expressed on a dry matter (DM) basis of pasture grab samples collected throughout pregnancy from the pregnancy maintenance (PM) and *ad-libitum* (AL) nutritional treatments (least squares means \pm SEM).

Nutritional treatments	<i>n</i>	NDF ¹	ADF ²	SSS ³	ME ⁴
AL	9	32.32 \pm 0.94	19.58 \pm 0.39	11.70 \pm 1.38	12.54 \pm 0.11
PM	9	31.50 \pm 0.94	18.45 \pm 0.39	13.06 \pm 1.38	12.36 \pm 0.11

SEM, standard error of the mean.

¹ NDF: neutral detergent fibre (g/kg DM); ² ADF: acid detergent fibre (g/kg DM); ³ SSS: soluble sugars and starch (g/kg DM); ⁴ ME: metabolizable energy. (MJ ME/kg DM).

5.4.2 Ewe live weight

The pregnancy live weight trajectory of the ewes in each nutritional treatment group is shown in Figure 29. Ewe live weights did not differ between treatments ($p > 0.05$) before the

commencement of the trial at P-2 (Table 13). Soon after the nutritional treatments started (from P0 to P5) there was a drop in live weight in the C (6.65 kg), AL50-100 (7.19 kg) and AL100-140 ewes (6.28 kg) so that by P50, their weight did not differ ($p>0.05$), but was considerable lower ($p<0.001$) than for ewes in AL0-50, AL0-100 and AL0-140, which, in turn, did not differ ($p>0.05$). At P100, ewes in AL0-100 and AL0-140 did not differ in live weight ($p>0.05$) but were heavier ($p<0.001$) than ewes in the other nutritional treatments. While, AL100-140 and C ewes were lighter ($p<0.05$) than AL0-50 ewes; with ewes in the former treatments being lighter than AL50-100 ewes. Again, a decrease in live weight was observed (Figure 29) after P100 in AL50-100 (6.85 kg) and AL0-100 (6.49 kg) ewes. At P140, AL0-50 and C ewes did not differ ($p>0.05$) in live weight and were lighter ($p<0.05$) than AL50-100, AL100-140 and AL0-100 ewes, which in turn did not differ ($p>0.05$) in live weight. At P140, AL0-140 ewes were heavier ($p<0.001$) than all other nutritional treatments.

At L20 (see Table 14), C ewes were lighter ($p<0.05$) than AL50-100, AL100-140, AL0-100 and AL0-140 ewes, but did not differ ($p>0.05$) from AL0-50 ewes. AL0-140 ewes were heavier ($p<0.001$) than AL0-50, AL50-100 and AL100-140 ewes, but did not differ ($p>0.05$) from AL0-100 ewes, which in turn did not differ ($p>0.05$) in live weight from any of the short-term nutritional treatments (AL0-50, AL50-100 and AL100-140). At L64 and L97, AL0-100 and AL0-140 ewes were heavier ($p<0.05$) than C ewes, but did not differ ($p>0.05$) from AL0-50, AL50-100 or AL100-140 ewes, which in turn, did not differ ($p>0.05$) in live weight from the control treatment ewes. Between L48 and L82, ewes that reared a singleton lamb (i.e. only one lamb of the set survived to this point) were heavier ($p<0.001$) than those ewes rearing a full set of twins.

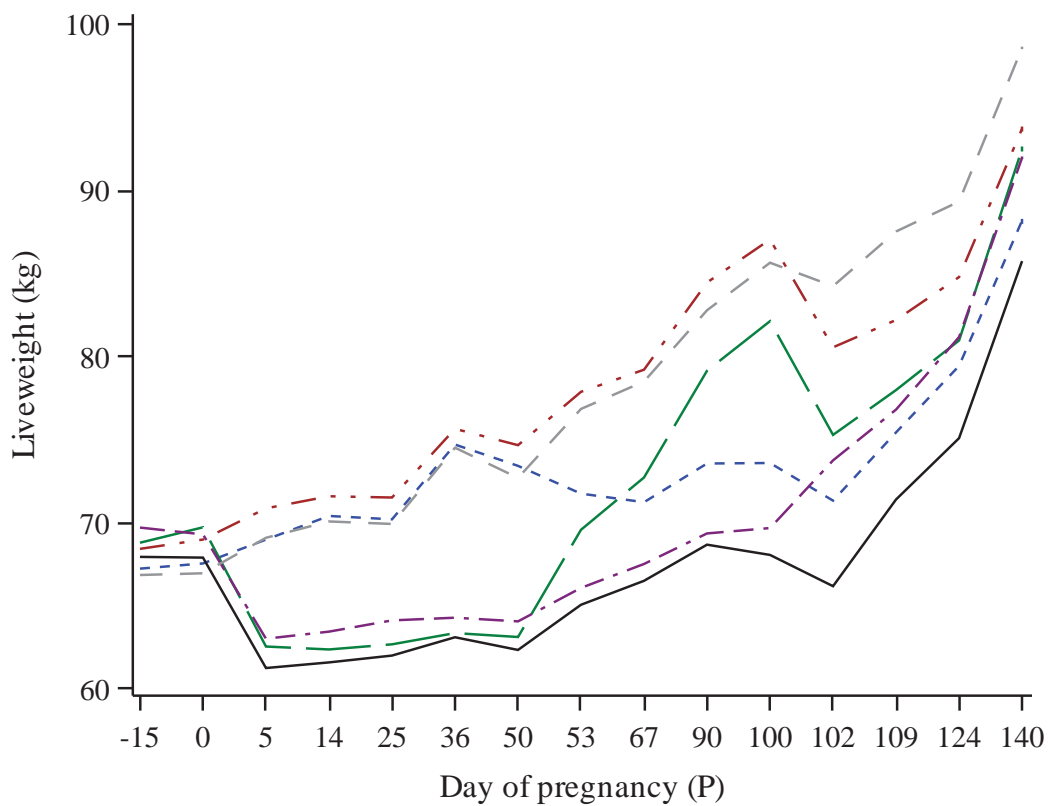


Figure 29. Live weight trajectory of ewes in the six nutritional treatments throughout pregnancy. Each nutritional treatment is represented by a different line and colour: AL0-50, early-pregnancy ad-libitum (AL) feeding from pregnancy day 1 (P1) to P50 (---; blue); AL50-100, mid-pregnancy AL feeding P50-P100 (— —; green); AL100-140, late-pregnancy AL feeding P100-P140 (- - • - -; purple); AL0-100, early- and mid-pregnancy AL feeding P1-P100 (-••-••; red); T140, pregnancy AL feeding P1-P140 (- -; grey), and; Control, pregnancy maintenance P1-P140 (—; black). Outside the aforementioned AL feeding periods ewes were offered the same pasture allowance as control ewes.

Table 13. Effect of ewe nutritional treatment on ewe live weight (kg) prior to artificial insemination (AI; at P-2) and in pregnancy (least squares means \pm SEM).

Nutritional treatments ¹	n	Ewe live weight during pregnancy			
		P-2*	P50	P100	P140
AL0-50	29	67.53 \pm 1.18	73.41 \pm 1.16 ^b	73.58 \pm 1.24 ^b	88.17 \pm 1.32 ^a
AL50-100	32	69.71 \pm 1.15	63.10 \pm 1.12 ^a	82.12 \pm 1.20 ^c	92.49 \pm 1.28 ^b
AL100-140	32	69.28 \pm 1.15	64.04 \pm 1.12 ^a	69.66 \pm 1.20 ^a	91.96 \pm 1.28 ^b
AL0-100	31	68.97 \pm 1.17	74.65 \pm 1.14 ^b	87.03 \pm 1.23 ^d	93.71 \pm 1.30 ^b
AL0-140	31	66.94 \pm 1.17	72.68 \pm 1.14 ^b	85.64 \pm 1.22 ^d	98.57 \pm 1.30 ^c
Control	33	67.88 \pm 1.15	62.32 \pm 1.12 ^a	68.04 \pm 1.20 ^a	85.74 \pm 1.28 ^a

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

*Weighing occurred over a two-day period and a proportion of animals in each treatment were weighed on either day.

^{abcd} Estimates within columns with different superscript differ significantly with at least $p < 0.05$. The absence of superscript indicates that $p > 0.05$.

Table 14. Effect of ewe nutritional treatment on their live weights (kg) in lactation (least squares means \pm SEM).

Nutritional treatments ¹	Ewe live weight post-lambing					
	<i>n</i>	L20	<i>n</i>	L64	<i>n</i>	L97
AL0-50	24	81.41 \pm 1.70 ^{ab}	24	84.95 \pm 1.89 ^{ab}	24	82.45 \pm 2.49 ^{ab}
AL50-100	31	82.81 \pm 1.56 ^b	30	84.28 \pm 1.74 ^{ab}	30	83.08 \pm 2.28 ^{ab}
AL100-140	25	82.03 \pm 1.71 ^b	25	84.93 \pm 1.84 ^{ab}	25	84.00 \pm 2.43 ^{ab}
AL0-100	28	84.65 \pm 1.55 ^{bc}	28	87.33 \pm 1.72 ^b	28	87.23 \pm 2.25 ^b
AL0-140	27	87.71 \pm 1.68 ^c	26	89.63 \pm 1.90 ^b	25	86.99 \pm 2.59 ^b
Control	32	77.46 \pm 1.53 ^a	32	80.99 \pm 1.70 ^a	32	80.61 \pm 2.22 ^a

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

^{abc} Estimates within columns with different superscript differ significantly with at least $p < 0.05$.

5.4.3 Ewe body condition score

Body condition score did not differ ($p>0.05$) across treatments before the commencement of the experiment at P-2 (Table 15, Figure 30). At P50, ewes in AL0-50, AL0-100 and AL0-140 treatments did not differ ($p>0.05$) in BCS, but they had greater BCS ($p<0.05$) than AL50-100, AL100-140 and C ewes, which in turn, did not differ ($p>0.05$). At P100, ewes in AL0-100 and AL0-140 had greater BCS ($p<0.001$) than all other treatments. Ewes in AL100-140 did not differ ($p>0.05$) from C ewes. Ewes in AL0-50 had greater BCS ($p<0.05$) than C ewes but were lower ($p<0.05$) than AL50-100 ewes. At P140, AL0-140 ewes had greater BCS ($p<0.001$) than all other treatments. In contrast, C ewes had the lowest BCS and differed ($p<0.05$) from all treatments except AL0-50. Ewes in AL100-140 and AL0-100 did not differ ($p>0.05$) in BCS at P140 but were greater ($p<0.05$) than AL0-50. AL50-100 ewes had lower BCS ($p<0.05$) than AL100-140.

At L20, the BCS of ewes in the short-term nutritional treatments (AL0-50, AL50-100 and AL100-140) did not differ ($p>0.05$; Table 16) from C ewes. Ewes in the AL0-140 treatments had greater BCS ($P<0.05$) than ewes in the control and short-term nutritional treatments, but did not differ ($p>0.05$) from AL0-100 ewes. In addition, AL0-100 ewes had greater BCS ($p<0.05$) than C and AL50-100 ewes but their BCS did not differ ($p>0.05$) from AL0-50 and AL100-140 treatments. At L64, AL0-140 treatments had greater BCS ($p<0.05$) than ewes in the control and short-term nutritional treatments, but did not differ ($p>0.05$) from AL0-100 ewes. All other nutritional treatments did not differ ($p>0.05$) in their BCS. At L97, AL0-140 ewes had greater BCS ($p<0.05$) than all other treatments, which in turn, did not differ ($p>0.05$). Ewes in the AL0-100 treatment had greater BCS

($p < 0.05$) than C, AL0-50 and AL0-140 ewes but did not differ ($p > 0.05$) from AL50-100 and AL0-140.

Table 15. Effect of ewe nutritional treatment on ewe body condition scores (BCS) prior to artificial insemination (AI, at P-2) and in pregnancy (least squares means \pm SEM).

Nutritional treatments ¹	<i>n</i>	Body condition score (0 – 5 scale)			
		P-2*	P50	P100	P140
AL0-50	29	2.82 \pm 0.24	3.77 \pm 0.24 ^b	2.73 \pm 0.24 ^b	2.87 \pm 0.25 ^{ab}
AL50-100	32	3.00 \pm 0.24	2.65 \pm 0.23 ^a	3.40 \pm 0.24 ^c	3.06 \pm 0.25 ^{bc}
AL100-140	32	2.90 \pm 0.24	2.71 \pm 0.23 ^a	2.38 \pm 0.24 ^a	3.46 \pm 0.25 ^d
AL0-100	31	3.00 \pm 0.24	3.99 \pm 0.23 ^b	4.12 \pm 0.24 ^d	3.39 \pm 0.25 ^{cd}
AL0-140	31	3.00 \pm 0.24	3.82 \pm 0.23 ^b	4.13 \pm 0.24 ^d	4.38 \pm 0.25 ^e
Control	33	2.95 \pm 0.24	2.78 \pm 0.23 ^a	2.47 \pm 0.24 ^{ab}	2.53 \pm 0.25 ^a

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

*Weighing occurred over a two-day period and a proportion of animals in each treatment were weighed on either day.

^{abcd} Estimates within columns with different superscript differ significantly with at least $p < 0.05$. The absence of superscript indicates $p > 0.05$.

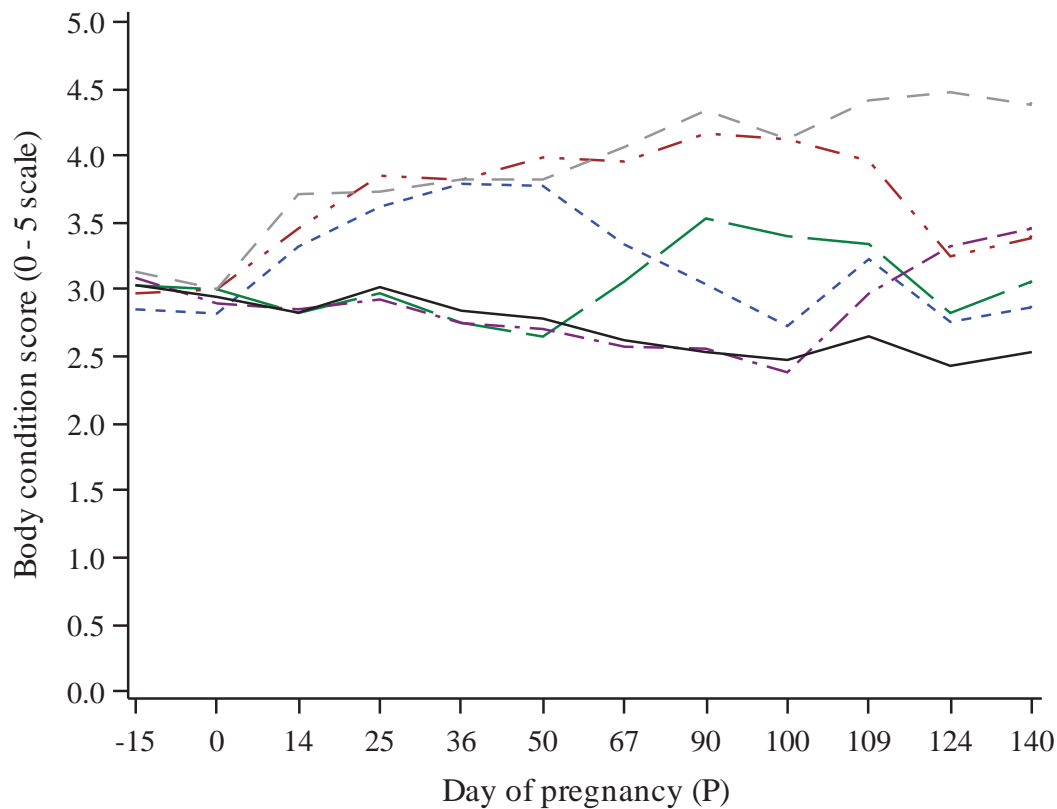


Figure 30. Body condition score (BCS) trajectory of the ewes in the six nutritional treatments throughout pregnancy. Each nutritional treatment is represented by a different line and colour: AL0-50, early-pregnancy ad-libitum (AL) feeding from pregnancy day 1 (P1) to P50 (---; blue); AL50-100, mid-pregnancy AL feeding P51-P100 (— —; green); AL100-140, late-pregnancy AL feeding P101-P140 (- - • - -; purple); AL0-100, early- and mid-pregnancy AL feeding P1-P100 (-••-••; red); T140, pregnancy AL feeding P1-P140 (- -; grey), and; Control, pregnancy maintenance P1-P140 (—, black). Outside the aforementioned AL feeding periods ewes were offered the same pasture allowance as the control treatment.

Table 16. Effect of ewe nutritional treatment during pregnancy on ewe body condition scores (BCS) in lactation (least squares means \pm SEM).

Nutritional treatments ¹	Ewe body condition score post-lambing							
	<i>n</i>	L20	<i>n</i>	L64	<i>n</i>	L97	<i>n</i>	L97
AL0-50	24	2.89 \pm 0.23 ^{ab}	24	2.82 \pm 0.21 ^a	24	3.19 \pm 0.23 ^a	24	3.19 \pm 0.23 ^a
AL50-100	31	2.83 \pm 0.22 ^a	30	2.76 \pm 0.20 ^a	30	3.32 \pm 0.22 ^{ab}	30	3.32 \pm 0.22 ^{ab}
AL100-140	25	2.93 \pm 0.23 ^{ab}	25	2.83 \pm 0.20 ^a	25	3.30 \pm 0.22 ^a	25	3.30 \pm 0.22 ^a
AL0-100	28	3.19 \pm 0.22 ^{bc}	28	3.04 \pm 0.20 ^{ab}	28	3.69 \pm 0.21 ^{bc}	28	3.69 \pm 0.21 ^{bc}
AL0-140	27	3.52 \pm 0.23 ^c	26	3.24 \pm 0.21 ^b	25	3.71 \pm 0.23 ^c	25	3.71 \pm 0.23 ^c
Control	32	2.85 \pm 0.22 ^a	32	2.78 \pm 0.20 ^a	32	3.16 \pm 0.21 ^a	32	3.16 \pm 0.21 ^a

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

^{abc} Estimates within columns with different superscript differ significantly with at least $p < 0.05$.

5.4.4 Gestation length

Ewes in AL0-140 had shorter gestation length ($p < 0.05$) than all other treatments (Table 17). Ewes in the control treatment had a longer gestation length ($p < 0.05$) than ewes in AL100-140; although both of these treatments did not differ in gestation length ($p > 0.05$) from AL0-50, AL50-100 and AL0-100. Lambing rate was greater ($p < 0.05$) for ewes in the AL0-140 treatment compared to all other treatments. In addition, the lambing rate of ewes in the AL100-140 treatment was greater than in C ewes. However, these two treatments did not differ ($p > 0.05$) from AL0-50, AL50-100 and AL0-100 treatments.

Table 17. Effect of ewe nutritional treatment on ewe gestation length (least squares means \pm SEM) and the proportion of ewes lambing by day 149.

Nutritional treatments ¹	<i>n</i>	Gestation length	Lambing rate at day 149 (%) [†]
AL0-50	29	148.65 \pm 0.45 ^{bc}	-0.44 \pm 0.56 (39%) ^{ab}
AL50-100	32	148.64 \pm 0.44 ^{bc}	-0.44 \pm 0.54 (39%) ^{ab}
AL100-140	32	148.31 \pm 0.44 ^b	-0.24 \pm 0.54 (56%) ^b
AL0-100	31	148.73 \pm 0.44 ^{bc}	-0.39 \pm 0.54 (40%) ^{ab}
AL0-140	31	146.54 \pm 0.45 ^a	1.50 \pm 0.61 (82%) ^c
Control	33	149.30 \pm 0.44 ^c	-1.09 \pm 0.57 (25%) ^a

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

[†] Logit probability estimates with standard errors and back transformed percentage in brackets.

^{abc} Estimates within columns with different superscript differ significantly with at least $p < 0.05$.

5.4.5 Lamb data

Lamb birth weight, CRL, CC and total litter weight at birth did not differ ($p>0.05$) across nutritional treatments (Table 18). Lambs born to ewes in the AL0-140 treatment had longer FL ($p<0.05$) than lambs born to ewes in all other nutritional treatments. Additionally, they had shorter RL ($p<0.05$) than lambs born to C and AL100-140 ewes. All other nutritional treatments did not differ ($p>0.05$) in either FL or RL. Male lambs were heavier (5.31 ± 0.16 vs 5.11 ± 0.16 , $p<0.05$) and had longer front (29.85 ± 0.30 vs 29.44 ± 0.30 , $p<0.05$) and rear legs (35.89 ± 0.32 vs 35.05 ± 0.33 , $p<0.001$) than female lambs but did not differ ($p>0.05$) in CRL and CC.

When gestation length was used as a covariate, differences in FL and total litter weight were observed (Table 19); however, there was still no difference ($p>0.05$) across treatments for lamb birth weight, CRL, CC and also for HL. Lambs born to ewes in the AL0-140 treatment had longer FL ($p<0.05$) than lambs born to ewes in all other nutritional treatments. Total litter weight did not differ ($p>0.05$) between C, AL0-50, AL50-100, AL100-140, AL0-140 and C ewes. However, total litter weight was lower ($p<0.05$) in the AL0-100 treatment compared to AL50-100 and AL0-140 treatments, although it did not differ ($p>0.05$) from any other treatments.

Lamb live weights from L20 to L97 (Table 20 and Table 21) did not differ ($p>0.05$) across nutritional treatments. There was no difference ($p>0.05$) in the odds ratio for lamb mortality across treatments (Table 21). The percentage of lambs surviving to weaning and the combined litter weight at weaning was lower for lambs born to AL100-140 ewes ($p<0.05$) compared to AL50-100 ewes and tended ($p = 0.06$) to be lower than C ewes. There were no

other differences ($p > 0.05$) in lamb survival or total litter weight at weaning across treatments.

Table 18. Effect of ewe nutritional treatment on lamb birth weight, crown-rump-length (CRL), chest circumference (CC), front (FL) and rear (RL) leg length and total litter weight (least squares means \pm SEM).

Nutritional treatments ¹	Birth weight		Total litter weight*		Morphological measurements (cm)				
	n [†]	kg	n [†]	kg	CRL	CC	FL	RL	
AL0-50	57	5.28 \pm 0.19	28	10.51 \pm 0.36	51.66 \pm 0.83	40.98 \pm 0.54	29.64 \pm 0.39 ^a	35.65 \pm 0.44 ^{ab}	
AL50-100	64	5.28 \pm 0.18	32	10.58 \pm 0.35	51.99 \pm 0.82	40.71 \pm 0.52	29.55 \pm 0.38 ^a	35.54 \pm 0.43 ^{ab}	
AL100-140	64	5.21 \pm 0.18	32	10.42 \pm 0.36	52.29 \pm 0.82	40.61 \pm 0.52	29.61 \pm 0.38 ^a	36.01 \pm 0.43 ^b	
AL0-100	60	5.10 \pm 0.18	29	10.08 \pm 0.36	51.83 \pm 0.82	40.64 \pm 0.53	29.33 \pm 0.38 ^a	35.21 \pm 0.43 ^{ab}	
AL0-140	62	5.12 \pm 0.18	31	10.29 \pm 0.36	51.80 \pm 0.82	40.18 \pm 0.53	30.64 \pm 0.38 ^b	34.72 \pm 0.43 ^a	
Control	66	5.29 \pm 0.18	33	10.58 \pm 0.35	51.88 \pm 0.82	40.77 \pm 0.52	29.12 \pm 0.38 ^a	35.67 \pm 0.43 ^b	

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

[†] Incomplete data from one set of twins in AL0-50 and two sets in AL0-100 were included for estimation of overall birth weight differences between treatments. However, these data were not used to estimate total litter weight differences across treatments.

* Refers to the combined weight of both lambs in a set per individual ewe.

^{ab} Least-squared means within columns with different superscript differ significantly by at least $p < 0.05$. The absence of superscripts indicates that $p > 0.05$.

Table 19. Effects of ewe nutritional, with gestation length as a covariate on lamb birth weight, crown-rump-length (CRL), chest circumference (CC), front (FL) and rear (RL) leg length and total litter weight (least squares means \pm SEM).

Nutritional treatments ¹	Birth weight		Total litter weight [*]		Morphological measurements (cm)					
	n [†]	kg	n [†]	kg	CRL	CC	FL	RL	FL	RL
AL0-50	57	5.23 \pm 0.16	28	10.42 \pm 0.29 ^{ab}	51.51 \pm 0.71	40.80 \pm 0.47	29.62 \pm 0.38 ^a	35.56 \pm 0.39	29.62 \pm 0.38 ^a	35.56 \pm 0.39
AL50-100	64	5.25 \pm 0.16	32	10.51 \pm 0.28 ^b	51.87 \pm 0.69	40.58 \pm 0.45	29.54 \pm 0.37 ^a	35.45 \pm 0.37	29.54 \pm 0.37 ^a	35.45 \pm 0.37
AL100-140	64	5.21 \pm 0.16	32	10.43 \pm 0.28 ^{ab}	52.32 \pm 0.69	40.61 \pm 0.45	29.61 \pm 0.37 ^a	36.07 \pm 0.37	29.61 \pm 0.37 ^a	36.07 \pm 0.37
AL0-100	60	5.03 \pm 0.16	29	9.95 \pm 0.29 ^a	51.62 \pm 0.70	40.43 \pm 0.46	29.32 \pm 0.38 ^a	35.08 \pm 0.38	29.32 \pm 0.38 ^a	35.08 \pm 0.38
AL0-140	62	5.34 \pm 0.17	31	10.74 \pm 0.29 ^b	52.58 \pm 0.71	40.97 \pm 0.48	30.69 \pm 0.39 ^b	35.38 \pm 0.40	30.69 \pm 0.39 ^b	35.38 \pm 0.40
Control	66	5.17 \pm 0.16	33	10.32 \pm 0.28 ^{ab}	51.45 \pm 0.69	40.32 \pm 0.45	29.09 \pm 0.37 ^a	35.35 \pm 0.37	29.09 \pm 0.37 ^a	35.35 \pm 0.37

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

[†] Incomplete data from one set of twins in AL0-50 and two sets in AL0-100 were included for estimation of overall birth weight differences between treatments. However, these data were not used to estimate total litter weight differences across treatments.

^{*} Refers to the combined weight of both lambs in a set per individual ewe.

^{ab} Least-squares means within columns with different superscript differ significantly by at least $p < 0.05$. The absence of superscripts indicates that $p > 0.05$.

Table 20. Effect of ewe nutritional treatment during pregnancy on lamb live weights (kg) during lactation (least squares means \pm SEM).

Nutritional treatments ¹	Lamb live weight post-birth							
	<i>n</i>	L20	<i>n</i>	L48	<i>n</i>	L64	<i>n</i>	L82
AL0-50	45	11.65 \pm 0.58	45	18.85 \pm 0.65	45	23.99 \pm 0.65	45	29.19 \pm 0.91
AL50-100	58	11.36 \pm 0.56	56	19.69 \pm 0.61	57	24.95 \pm 0.60	57	30.22 \pm 0.87
AL100-140	47	11.53 \pm 0.58	44	19.58 \pm 0.64	44	24.61 \pm 0.64	44	29.94 \pm 0.91
AL0-100	48	11.74 \pm 0.56	47	19.91 \pm 0.62	48	24.54 \pm 0.62	48	30.15 \pm 0.88
AL0-140	48	11.93 \pm 0.58	47	19.54 \pm 0.65	47	24.43 \pm 0.65	47	29.85 \pm 0.92
Control	58	11.59 \pm 0.56	58	19.53 \pm 0.61	58	24.64 \pm 0.60	58	29.96 \pm 0.87

SEM, standard error of the mean.

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

The absence of superscripts indicates $p > 0.05$.

Table 21. Effect of ewe nutritional treatments during pregnancy on lamb weaning weight, total litter weight at weaning (least squares means \pm SEM) and lamb survival.

Nutritional treatments ¹	Weaning weight		Total litter live weight		Lamb survival	
	<i>n</i>	kg	<i>n</i>	kg	Probability [†] (95%CI)	Odds ratio (95%CI) [*]
AL0-50	45	31.91 \pm 0.94	29	48.40 \pm 4.63 ^{ab}	82 (65 – 92) ^{ab}	0.65 (0.20 – 2.11)
AL50-100	56	33.06 \pm 0.90	32	56.70 \pm 4.46 ^b	89 (75 – 95) ^b	1.14 (0.33 – 3.85)
AL100-140	44	32.62 \pm 0.94	32	44.97 \pm 4.47 ^a	71 (53 – 85) ^a	0.35 (0.12 – 1.06)
AL0-100	46	33.21 \pm 0.91	31	48.70 \pm 4.51 ^{ab}	79 (61 – 90) ^{ab}	0.53 (0.17 – 1.67)
AL0-140	46	32.66 \pm 0.97	31	48.68 \pm 4.72 ^{ab}	77 (58 – 88) ^{ab}	0.47 (0.15 – 1.46)
Control	57	32.92 \pm 0.90	33	55.19 \pm 4.48 ^{ab}	87 (74 – 95) ^{ab}	–

SEM, standard error of the mean

¹ Nutritional treatments: AL0-50 = maternal AL feeding from AI to P50; AL50-100 = maternal AL feeding from P51 to P100; AL100-140 = maternal AL feeding from P101 to P140; AL0-100 = maternal AL feeding from AI to P100; AL0-140 = maternal AL feeding from AI to P140; Control = pregnancy maintenance from AI-P140. Outside the aforementioned AL feeding periods, ewes were offered the same pasture allowance as the control treatment.

[†] Back transformed mean survival percentage in the probability scale.

^{ab} Estimates within columns with different superscript differ significantly ($p < 0.05$). The absence of superscript indicates $p > 0.05$.

^{*} For odds ratio estimates, 95% confidence interval that cross 1 indicates that each individual treatment did not differ ($p > 0.05$) from the control.

5.5 Discussion

The present study focused on offering twin-bearing ewes an *ad-libitum* pasture allowance at different times and for different lengths to determine the effect of these nutritional regimens on the ewe and her lambs. Overall, the results of the present study demonstrate that short- and long-term *ad-libitum* feeding increased the live weight and BCS of twin-bearing ewes for a short period at least. However, *ad-libitum* feeding at the various stages and lengths did not increase lamb birth weights and weaning weights.

It was apparent that after the first live weight measurement or after changes in feeding level (i.e. after day 50 and 100), the live weight of some ewe groups changed dramatically. These variations are likely explained by changes in gut fill due to changes in feeding level. It has previously been reported that rumen contents can account for 10% to 23% of total ewe live weight (Hughes, 1976). Nevertheless, the pasture masses measured and the ewe live weight and BCS during pregnancy indicated that the feeding treatments utilised were successful in increasing ewe LW and BCS during the manipulation period. Similarly, the live weight and BCS trajectories of C ewes indicate that PM feeding was successfully attained. From P1 (i.e. after PM commenced) to P50, there was only a marginal increase in C ewe LW. During the next 50 days, C ewe LW increased by 5.7 kg, which is similar to the conceptus mass reported by Rattray et al. (1974) at P100. The total increase in C ewe LW from P-2 to P140 of 17.9 kg is comparable to previously reported conceptus mass and gravid uterus weight for twin-bearing ewes of 15 kg to 17 kg at P140 (Rattray et al. 1974; Kenyon et al. 2007). These results firstly indicate that the C treatment was successful at meeting its total change in ewe live weight objective and secondly demonstrates the adequacy of the provided pre- and post-grazing feeding masses to achieve this.

Short- and long-term maternal AL feeding improved the live weight and BCS of ewes during pregnancy, for a short period at least, but did not alter the lamb birth weight compared to lambs born to control fed ewes. The absence of a significant effect on birth weight is in agreement with previous studies (Morris and Kenyon, 2004; Corner et al. 2008; Kenyon et al. 2011, 2012 and Corner-Thomas et al. 2015) using similar pasture allowances. However, during pregnancy, AL treatment ewes failed to maintain their LW and BCS advantage after the period of AL feeding (they lost BCS) when returned to a PM feeding level. This suggests that the pasture allowance provided to the C ewe was insufficient to meet the PM requirements of the heavier AL treatment ewes post-manipulation (see BCS, Figure 3). Potentially, this level of feeding after an AL period could have outweighed any potential positive effects due to AL feeding.

Little effects of the maternal feeding treatments were observed on lamb live weights post-birth. Gibbs and Treacher (1982) reported that under adequate pasture conditions during lactation, differences in ewe BCS at lambing did not affect milk production; whereas, if feeding conditions were sub-optimal during lactation, effects might be observed. Therefore, it is not surprising that pregnancy feeding treatment effects on lamb live weight were not observed given the pasture masses in lactation. Schreurs et al. (2012) in their meta-analysis of individual animal data across seven experiments reported that whilst ewe lamb live weight during gestation influenced lamb birth weight and weaning weight, overall effects were small. Similarly, the combined results from the meta-analyses in Chapters 2, 3 and 4 and previous narrative reviews (Kenyon and Blair, 2014; Bell and Greenwood, 2016) suggest that maternal feeding above PM requirements has only a small positive effect on lamb weaning weight. Combined, the results indicate there is no advantage of feeding adult

ewes above their PM requirements, independent of stage of pregnancy as it does not improve the weight of their lambs to weaning under normal feeding conditions. However, studies should examine potential impacts when feeding conditions in lactation are suboptimal.

Above pregnancy nutrition during late-pregnancy only or throughout pregnancy resulted in a decrease in gestation length of 1 and 3 days, respectively, compared to C ewes. The decrease in gestation length, especially in the AL0-140 ewes is comparable to those obtained by Holst et al. (1986), Wallace et al. (2005), Ford et al. (2009) and Zhu et al. (2009). It is difficult to elucidate a mechanism responsible for this decrease in gestation length. Gestation length can be affected by both genetic and environmental effects (Clegg, 1959), with the maternal diet being one of many environmental effects that can shorten gestation length (Forbes, 1967). It has been hypothesised that elevated fetal blood cortisol concentrations of overnourished ewes may play a role (Ford et al. 2009) or that placental progesterone metabolism may be impaired as a result of high feed intakes (Wallace et al. 2005), thereby leading to a shorter gestation length. These measurements, however, were not explored in the present experiment and the shorter gestation length remains unexplained, but may warrant further examination.

Despite the shorter gestation length in AL0-140 ewes, individual lamb birth weight and total litter weight was similar to control lambs, even after adjusting for gestation length differences (Table 9). This suggests that fetal growth at some point during pregnancy was enhanced in lambs born to AL0-140 ewes compared to controls, but was not detectable at the current sample size. Nonetheless, adjusting total litter weight for gestation length

revealed that lambs from AL0-140 and AL50-100 ewes were heavier than those from AL0-100 ewes. This is likely the result of the insufficient pasture allowances (i.e. at a C level) provided to the heavier AL ewes post-manipulation. Whilst both, AL50-100 and AL0-100 ewes, were affected by the pasture allowance provided in late-pregnancy, AL0-100 ewes were heavier than AL50-100 ewes on P100 and the degree of BCS loss due to the insufficient feeding in late-pregnancy was therefore greater in AL0-100 ewes (Table 5), which may have slightly impaired fetal growth in their lambs.

The mean birth weights across all treatments were within the optimal range for lamb survival (Dalton et al. 1980; Everett-Hincks and Dodds, 2008; Oldham et al. 2011) and nutritional treatments did not change lamb birth weight. Therefore, it might be expected that no effect on survival would be observed. Indeed, lamb survival was not affected by the increased maternal nutrition. However, AL100-140 treatment lambs were less likely to survive than AL50-100 lambs. This survival difference was further evident in total litter weight at weaning (which takes into account both lamb growth and survival). Reduced lamb survival due to AL feeding during late-pregnancy has not been previously observed in adult ewes. While overnourishment in ewe lambs (Wallace et al. 2006; Swanson et al. 2008) resulted in reduced colostrum quality and quantity and lower lamb vigour. The present result combined with ewe lamb data suggests further examination as to the cause of lower survival in mature ewes is required. Some caution is advised when interpreting the present survival data due to the number of lambs in each group. The largest difference in lamb survival in this study was 18% (e.g. AL50-100 vs. AL100-140; Table 11). Statistical power at the current sample sizes to determine a difference in 18% in survival probability was only 62%.

5.6 Conclusion

This study aimed to determine whether *ad-libitum* feeding over various periods of pregnancy would result in heavier lambs at birth and at weaning when compared to lambs born to ewes fed to pregnancy maintenance requirements. Irrespective of the stage of pregnancy, AL feeding successfully increased twin-bearing ewe live weight and BCS, but did not increase lamb birth weight or their weight during the pre-weaning period. Therefore, there is no benefit, from a twin lamb live weight perspective, from offering the ewe a level of nutrition above pregnancy maintenance. Further, there is evidence to suggest that *ad-libitum* feeding during late-pregnancy can negatively affect lamb survival.

5.7 References

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5.8 Supplementary material for Chapter 5

The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

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	ITEM	RECOMMENDATION	Section/ Paragraph
Title	1	Provide as accurate and concise a description of the content of the article as possible.	Page 371
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	Page 373
INTRODUCTION			
Background	3	<p>a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.</p> <p>b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.</p>	<p>Page 376, paragraph 1-2</p> <p>Page 377, paragraph 1</p>
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.	Page 377, paragraph 1
METHODS			
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.	Page 377, paragraph 2
Study design	6	<p>For each experiment, give brief details of the study design including:</p> <p>a. The number of experimental and control groups.</p> <p>b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when).</p> <p>c. The experimental unit (e.g. a single animal, group or cage of animals).</p> <p>A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.</p>	<p>Page 378, paragraph 1-2. Page 379, paragraph 1. See also Figure 27.</p>
Experimental procedures	7	<p>For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example:</p> <p>a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).</p> <p>b. When (e.g. time of day).</p> <p>c. Where (e.g. home cage, laboratory, water maze).</p> <p>d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).</p>	Page 380 - 381
Experimental animals	8	<p>a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range).</p> <p>b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.</p>	<p>Page 380, paragraph 1.</p> <p>Page 378, paragraph 2, Page 379.</p>

The ARRIVE guidelines. Originally published in *PLoS Biology*, June 2010¹

Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.	Page 381, paragraph 2 and Page 382 - 383. Not applicable
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant.	Page 382, paragraph 1. Page 378 - 379. Not applicable
Allocating animals to experimental groups	11	a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed.	Page 380 - 383
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).	Page 383 - 384
Statistical methods	13	a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.	Page 384 - Page 387
RESULTS			
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing. (This information can often be tabulated).	Page 388 - 391
Numbers analysed	15	a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50% ²). b. If any animals or data were not included in the analysis, explain why.	All tables Page 381 -
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).	All tables
Adverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.	Not applicable
DISCUSSION			
Interpretation/scientific implications	18	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results ² . c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.	Page 404 - 407. Not applicable
Generalisability/translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.	Not applicable
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.	Not applicable

Chapter 6: General Discussion

6.1 Introduction

Evidence over the past 100 years has demonstrated that the nutrition of the pregnant ewe can influence the development of the fetus, which in turn can have an impact on the lamb's birth weight and its growth to weaning. These parameters have a significant impact on economic efficiency in sheep production systems (Klaassen et al. 2015). The current pool of literature has also described many of the biological mechanisms via which maternal nutrition may influence fetal growth and development. Perhaps the most challenging task in reviewing the current pool of literature lies in comparing results from experiments that not only vary in the nutritional treatments imposed but also in many other factors (e.g. maternal breed, age, mature live weight, diet post-treatment, litter size, lamb sex and sample size); all of which can potentially contribute to the variability across experiments. Because of this complexity, no single study can provide definitive understanding of responses to a particular treatment (Lean et al. 2009) and there is value in combining the available evidence into a more global picture. Traditionally, narrative reviews have provided limited conclusions about the effects of changing the ewe nutrition during pregnancy on lamb growth. However, narrative reviews have highlighted some potential experimental factors that may be responsible for generating inconsistency in the measured effects across studies. The major limitation with this narrative approach is that the contribution of these factors to the variability in results across studies can only be hypothesised as the effects have not been quantified. There is a need to extrapolate this biological knowledge into quantifiable and predictable outcomes. Ultimately, is quantifiable evidence that will generate usable information for extension programs.

The work presented in this thesis introduces systematic review and meta-analysis as an alternative approach for the review of literature and the quantitative integration of results across experiments (Chapter 1). These methods were used to achieve three main objectives: firstly, to review the literature on the effect of maternal nutrition during pregnancy on fetal and lamb growth and to estimate how changes in ewe nutrition affected the weight of the resulting fetuses/lambs at three stages of their life: a) during the last six week of gestation (Chapter 2), b) at birth (Chapter 3) and c) at weaning (Chapter 4). Secondly, meta-analytic methods were used to quantify the amount of variation in study results and to determine the contribution of experimental factors responsible for this variation. Thirdly, results from these investigations helped identify areas of research that required further experimentation and a field trial (Chapter 5) was designed with the aim of providing increased understanding to one of these research areas. In the following sections of this general discussion chapter, the main findings of this thesis, some experimental considerations of the meta-analytic evidence, along with the methodological limitations of the present work are considered. In the last two sections, the practical implications of the present work for grazing sheep systems are discussed, along with future research considerations.

6.2 Summary of findings

Early reviews (Wallace, 1947; Blaxter, 1959; Reid, 1963; Robinson, 1977) explained the importance of the timing, length and severity of undernutrition in determining the magnitude of effects observed on fetal, birth and weaning weights. Since then, a vast number of studies have examined many variations in these three experimental factors and a large number of reviews have reached similar conclusions. In support of this literature, Chapter 2, 3 and 4 showed a general trend for undernutrition to result in an increasingly

negative effect on fetal/lamb weight, as pregnancy progressed and with an increasing length of the nutritional manipulation period. These three Chapters, however, shift the paradigm of reviews from narrative summaries of literature with dichotomous conclusions (i.e. effect or no effect) to quantitative integration of results.

6.2.1 Early- and mid-pregnancy undernutrition

Studies examining maternal undernutrition during the first 30 days of pregnancy that are usable for meta-analysis are scarce, especially studies conducted under pastoral conditions. To study this period of pregnancy, two experimental designs were combined throughout this thesis: periconceptional undernutrition (PCUN) and undernutrition during the first 30 days of pregnancy. The only conceptual and practical difference between these two experimental designs is that PCUN can (but not always) affect the ewe's body reserves prior to mating and thus it is desirable to understand whether this small change in experimental design could alter the ewe's response to undernutrition during the first 30 days of pregnancy. Across the selected studies, the effects of early-pregnancy undernutrition on late gestation fetal weight (LGFW), birth weight (BW) and weaning weight (WW) were, on average, very small and perhaps undetectable. In the absence of consistency in effects measured and with a meta-analytic mean showing a negligible effect, the present analysis suggests that limiting ewe intake during the first 30 days of pregnancy poses no consequence to the lamb, with regards to its LGFW, BW and WW.

Similarly, two experimental designs were studied to understand the effect the mid-pregnancy maternal undernutrition: early-to-mid and mid-pregnancy undernutrition. Whilst literature does exist, few studies were usable for meta-analysis. This limited evidence

showed no consistent pattern in responses to undernutrition across studies. Much of the inconsistency in results was related to differences in the length of undernutrition (early-to-mid vs. mid-pregnancy) and the level of nutrition during late-pregnancy (pregnancy maintenance vs. above). In general, however, effects were small in magnitude and even when severe undernutrition was employed, BW and WW responses did not exceed a decrease of 6% and 9%, respectively, in relation to their control counterparts. This suggests that any negative impact on the growth trajectory of the fetus as a result of mid-pregnancy undernutrition can be alleviated by providing the ewe with adequate nutrition to meet or surpass her requirements during late-pregnancy and lactation.

6.2.2 Late-pregnancy undernutrition

Two experimental designs were employed to understand the effect of late-pregnancy maternal undernutrition: undernutrition during late-pregnancy (day 90 or later until term) and long-term maternal undernutrition extending into late-pregnancy. This was undertaken in an attempt to understand whether ewes whose body reserves may have been affected prior to late-pregnancy (as in long-term undernutrition studies) would respond differently to ewes that started a nutritional stress in late-pregnancy without having experienced a decrease in live weight (LW) and body condition score (BCS). The combined results from Chapter 2 and 3 consistently demonstrated that undernutrition of the ewe in the last 8 to 6 weeks of pregnancy had negative impacts on the offspring. Fetal weight in late gestation was reduced, on average, by 766 grams, whilst BW decreased between 320 grams and 1.15 kg compared to controls. Even when nutrition did not limit ewe and lamb performance during the pre-weaning period, the data presented in Chapter 4 demonstrated that lambs born to ewes that were undernourished during late-pregnancy were between 9% and 18%

lighter than their controls suggesting that moderate to large residual effects were carried through to weaning. In addition, long-term undernutrition extending to late-pregnancy resulted in similar (Chapter 3) or more severe effects (Chapter 2 and 4) on the fetus/lamb.

The practical significance of these findings was concluded to be two-fold. Firstly, management decisions should be targeted to at least meet the minimum requirements for pregnancy in the last six weeks before lambing. Secondly, the way ewes respond to a limitation on their intake during the last six weeks of pregnancy depends upon their nutritional status at the commencement of late-pregnancy (i.e. whether they have previously been underfed). This highlights the importance of the nutrition of the flock pre-breeding and/or during early- and mid-pregnancy to achieve or maintain adequate body reserves prior to day 100 of pregnancy and also the necessity of monitoring BCS during late-pregnancy to track the adequacy of feeding regimens.

6.2.3 Ewe nutrition above the requirements for pregnancy

The meta-analytic evidence in the present work demonstrated that providing the ewe a level of nutrition above that required to maintain pregnancy was, on average, associated with a small increase in LGFW (singletons only), BW and WW. This meta-analytic approach was unable to determine a practical nutritional regimen that could be used to promote fetal and lamb growth. This was likely the consequence of a small number of studies looking at the effect of “overnutrition” or “above pregnancy maintenance feeding”. In addition, there was a lack of evidence for each stage of pregnancy and the interaction between length and timing of above pregnancy maintenance feeding. In an attempt to provide further understanding about this interaction, Chapter 5 showed that *ad-libitum* feeding of mixed-

age ewes at varying periods of pregnancy (day 0 (P0) to P50, P50 to P100, P100 to P140, P0 to P100 and P0 to P140) did not increase twin-lamb live weight from birth to weaning when compared to lambs born to ewes that were fed to meet their pregnancy maintenance (PM) requirements throughout pregnancy. In Chapter 5, providing twin-bearing ewes with *ad-libitum* (AL) feeding promoted considerable LW and BCS score gains relative to the control ewes. These AL-fed ewes, however, failed to maintain their LW and BCS advantage post-treatment, when offered a PM-level of feeding similar to the control group. Given the size of the estimated meta-analytic effects, the lack of effects on lamb live weight from birth to weaning and the relative increase in feed demand, it was concluded that increasing ewe intake beyond that required to meet pregnancy requirements is unjustified as a management tool to increase lamb and ewe performance during the pre-weaning period.

6.2.4 Important moderator variables

6.2.4.1 Length of undernutrition

Consistently with previous studies, the length of undernutrition influenced responses, with increasing lengths of undernutrition periods being associated with more severe negative effects. Whilst this is true as a general trend across meta-analyses, Chapter 3 demonstrated that longer-term nutritional manipulations extending into late-pregnancy do not always result in more severe effects when compared to undernutrition imposed in late-pregnancy only. This hints at the importance of the severity of undernutrition in determining the magnitude of an effect, irrelevant of the ewe's body reserves prior to late-pregnancy and confirms that different patterns of ewe LW change can result in a similar decrease in BW.

6.2.4.2 Litter size

The magnitude of the estimated effects for singletons and twins did not differ for LGFW, BW and WW. Potentially, the inadequate number of data points for one of the litter sizes was responsible for the absence of observed differences, especially at weaning. Indeed, many studies had to be excluded from the meta-analyses because the interaction between nutritional treatment and litter size was not statistically significant, which meant that outcomes for each litter size at each nutritional level (i.e. control and treatments) were not presented in the manuscript (only combined main effects were presented). The observation of a similar size effect, however, is sensible because both singleton and twin fetuses achieve a similar proportion of their BW at 8, 4 and 2 weeks prior to birth (Robinson, 1977) and has been previously reported in one large-scale experiment (Oldham et al. 2011). Therefore, a similar decrease in nutrient intake, relative to their own requirements and all other factors constant, will likely have similar consequences to the lamb in proportion to their potential size. For example, a similar size effect, such as a 500 grams decrease in BW, can be considered as being more detrimental to the potential performance and survival of a 4 kg twin lamb (representing a decrease of 12.5% in BW) compared to a 7 kg singleton (representing only a 7% decrease in BW). This highlights the importance of identifying singleton and multiple bearing ewes at pregnancy scanning and feeding those ewes accordingly to their pregnancy requirements.

6.2.4.3 Year of publication

Year of publication had a significant impact on the magnitude of BW responses to late-pregnancy undernutrition (Chapter 3). The diminishing magnitude of effects over time was likely the result of a greater awareness of animal ethics that started in the early 1950's and

caused a global change in animal ethics standards by the late 1980's (Sandoe and Christiansen, 2008). In meta-analysis, this is traditionally referred to as time-lag bias (Ioannidis, 2005). It was previously discussed that this time-lag bias was likely due to an inclination of early research towards nutritional manipulations that were known to have large effects on BW, whereas the magnitude of effects observed in studies published after 1994 appear to fluctuate between small to large effects. The problem with the time-lag bias found in Chapter 3 is that papers published later than 1994 show a more conservative picture about the effect of late-pregnancy undernutrition on BW than those published earlier. Clarke and Stewart (1998) proposed that to overcome a time-lag bias, meta-analyses should include studies that start before a specific point in time. This was not implemented in Chapter 3 as it would have meant a substantial loss of evidence. Nevertheless, it appears that at some point in time (likely around 1994) a shift in the paradigm occurred that focused not on finding BW effects but rather in understanding how various nutritional manipulations could lead to different patterns on fetal growth and thus, eventual BW.

6.2.4.4 Level of feeding of the control group

The level of feeding of control groups varied considerably between experiments. In the present study, two types of controls were found across the literature: 1) control ewes fed to meet their pregnancy maintenance requirements (PM-fed) and 2) control ewes fed above their pregnancy requirements (APM-fed). Feeding ewes above their pregnancy maintenance requirements was shown to have a small but significant effect on LGFW (singletons only), BW and WW. It was therefore expected that the level of feeding of the control group in relation to an undernourished group would explain some of the variation across studies. A better study design is to have three nutritional scenarios: 100% of PM, APM and

undernutrition (Table 22). In these studies, feeding ewes above their pregnancy requirements increased, decreased and had no effect on lamb birth weight relative to the PM fed ewes and thus, the magnitude of the effect of undernutrition in relation to PM-fed and APM-fed groups was also affected. However, using the level of feeding of the control groups as a predictor in meta-regression models resulted in small but non-significant effects, suggesting that any potential difference was not detectable with the number of studies available. This is important for two reasons: Firstly, the moderating effect of the levels of feeding of the control group in the present study cannot be ruled out given the fragmented nature of the data and further examination is required. Secondly, to date, the true effect of providing ewes with feeding levels above their pregnancy requirements is not well understood and care should be taken when undertaking undernutrition experiments in sheep using APM-fed ewes as controls since it creates unnecessary noise (i.e. unexplained variation) in the data that may lead to less accurate estimation of treatment effects.

Table 22. Birth weight data from nutritional studies in sheep in which three nutritional scenarios have been studied: pregnancy maintenance (PM), above pregnancy maintenance (APM) and undernutrition (UN). The difference in birth weight of the undernutrition groups was compared against PM and APM groups.

Reference	Birth weight (kg)			Difference in birth (grams)	
	PM [‡]	APM [§]	UN [‡]	vs. 100% PM	vs. APM
Annet & Carson, 2006 ^{ae}	7.34 ^a	6.41 ^a	6.73 ^a	-610	+320
	10.88 ^a	10.88 ^a	10.55 ^a	-330	-330
	13.13 ^a	13.69 ^a	13.00 ^a	-130	-690
Sen et al. 2013	4.28 ^a	4.21 ^a	3.74 ^b	-540	-470
Khanal et al. 2014	4.35 ^a	4.38 ^a	3.89 ^b	-460	-490
McGovern et al. 2015	4.71 ^a	4.87 ^a	4.65 ^a	-60	-220
Hoffman et al. 2016	4.82 ^a	5.78 ^b	4.61 ^a	-210	-1170

^{ae} Means represent total rather than individual lamb birth weight.

[‡] Ewes fed to meet 100% of their pregnancy requirements. [§] Ewes fed above their pregnancy requirements. [‡] Underfed ewes.

^{a,b} Within rows, means with different superscripts differ ($p < 0.05$)

6.3 Methodological considerations

Three important issues that arise from the available literature need consideration. Firstly, experiments measuring the effect of early- and mid-pregnancy undernutrition rely on a measurement that is obtained long after the period of stress (i.e. the nutritional manipulation). The studies selected for the meta-analyses in Chapters 2, 3 and 4 were carefully chosen so that nutrition outside the manipulation period was adequate to meet or surpass the ewe's nutritional requirements for pregnancy. This means that the period of active growth of the fetus in late gestation was not limited by the ewe nutrition. As a consequence, it may not be surprising that the effects of early- and mid-pregnancy

undernutrition on LGFW, BW and WW were small in magnitude and noticeable effects were only observed when severe undernutrition was imposed (i.e. during the periconceptual period and early-to-mid-pregnancy).

Secondly, if results are expected to be small in magnitude, the sample sizes used in these experiments must be adequate to accurately quantify the small effects with statistical precision. This is relevant because, often, conclusions tend to focus only on statistical significance to determine whether nutritional treatments had an “effect” or not on the lamb. Often the size of any observed, but non-significant, effects are disregarded. Table 23 puts this into perspective and looks at the statistical power of some studies used in Chapter 3; these studies are for example only, and is not a complete list. The evidence presented in Table 23 suggests that studies are often underpowered and that the ideal sample sizes needed to measure such small effects may not be achievable in practice, especially in biomedical research.

Table 23. Statistical power of some undernutrition studies that varied in the size of estimated effects and sample sizes. The sample size (n) for each group necessary to achieve a 50% and 90% power was also estimated using Cohen (1988) guidelines.

First author, year	BW difference relative to control	Hedges' g	Reported sample size in each group	Significance reported	Power*	n required for 50% power [§]	n required for 90% power [‡]
Everitt, 1967	-258	-0.34	21/13	S	15%	67	182
Gardner, 2005	-200	-0.23	5/5	NS	6%	146	398
Khan, 2005	+400	0.52	6/13	NS	17%	29	78
Oliver, 2005	-850	0.89	8/10	S	42%	11	27
Chadio, 2007	-350	-0.34	13/9	NS	12%	67	182
Hyatt, 2007	-430	-0.49	8/10	NS	16%	33	88
Jaquiere, 2011							
Single (males)	+900	1.02	8/13	NS	58%	NA	21
Single(females)	+500	0.67	15/13	NS	40%	18	48
Twin (males)	-300	-0.52	16/14	NS	28%	29	78
Twin (females)	-100	-0.14	24/21	NS	7%	393	1017
Single (pooled)	+750	0.88	23/26	NS	85%	NA	28
Twin (pooled)	-180	-0.27	40/35	S	21%	106	289
Kenyon, 2011	-140	0.18	134/120	NS	30%	238	650

* Refers to the statistical power to find a statistically significant effect given the observed effect, at the current sample sizes. [§]Sample size (n) is the number in each group necessary to achieve a power of 50%. [‡]Sample size (n) is the number in each group necessary to achieve a 90% power. NS = non-significant, S = Significant, NA = not applicable.

The third issue that arises from the experiments is that the experimental ewes in many of these studies can only be selected after pregnancy has been confirmed and the number of fetuses is known to the researchers. In some cases, ie., PCUN and early-pregnancy undernutrition, pregnancy diagnosis happens after the nutritional manipulation period has concluded. Thus, information regarding ovulation rates, embryo survival, placental growth and conception rates from the original number of ewe mated/inseminated is often not available (i.e. not measured) or not reported. Without this information, the process of selecting the experimental ewes cannot be evaluated for meta-analytic purposes. There will be a natural bias towards selecting animals that are either “hardy” enough to endure a particular level of undernutrition without pregnancy loss or that were best prepared, for example they had better BCS at the start of treatment, to tolerate some level undernutrition without pregnancy loss. In the absence of this information it is difficult to quantify a true production effect, as even in the absence of statistically significant effects on lamb birth weight, other production parameters cannot be adequately evaluated.

6.4 Limitations

6.4.1 Reporting details of primary studies

There are two limitations in relation to the inadequate reporting details of primary studies that affected the meta-analyses in Chapter 2, 3 and 4. Firstly, in many narrative reviews (Harding, 2001, Wu et al. 2006, Caton and Hess, 2010, Kenyon and Blair 2014, Bell and Greenwood, 2016) and throughout this thesis, it is acknowledged that variations in the severity of the nutritional manipulations imposed is likely responsible for much of the variation in responses observed across experiments. Generally, very severe undernutrition results in very large effects and consequently “exaggerated” effect sizes, whilst on the

contrary, very mild undernutrition often results in either no effect observed or very small effect sizes. This is particularly amplified in studies with low sample size. However, information regarding the energetic level of nutritional manipulations imposed is rarely reported in the literature. In the absence of a predictor variable that can provide information on how different levels of undernutrition affect the fetus/lamb this cannot be quantified. It could be argued that from a production perspective, the severity of undernutrition is rarely, if at all, known to the farmer in terms of energetic levels. However, measurements of LW and BCS are readily available to the farmer and they can be used as indicators of nutritional inadequacy. In the absence of this essential information in primary studies, many questions remain unanswered that limit the development of nutritional guidelines for sheep farmers beyond those already established.

The second limitation of Chapters 2, 3 and 4 is that the number of reviewed studies does not match the actual number of studies undertaken in the area, as indicated earlier. Rather than a meta-analysis methodological issue, this limitation arises from the inadequate reporting detail of basic experimental information including: 1) randomization of experimental animals, 2) sample sizes, 3) litter type used for experimentation, 4) measurements of error of treatment means and 5) important interactions (as previously discussed) and 6) whether the reported animals are a cohort of a previously reported experiment. Without some of this basic information, effect sizes cannot be estimated for individual studies and thus these studies cannot be used for meta-analytic purposes. In their “raw” form, individual studies are hardly comparable to each other. It is only when combined as effect sizes, that dissimilar studies can be integrated in evidence-based models. Despite the above, a large number of studies did not meet the criteria for inclusion

selected for this study. Therefore, a great deal of information was, inevitably, not included in the meta-analyses and could have potentially affected the accuracy and magnitude of the calculated estimates.

6.4.2 Conception rate, ewe live weight and BCS achieved in Chapter 5

During the design of the experiment reported in Chapter 5, power analysis was carried out to determine an adequate sample size to determine an effect hypothesised to range between 300 and 500 grams across six treatments relative to the control group. The first limitation of this experiment was the unexpected low conception rate (52%) obtained after artificial insemination of nearly 800 ewes. This reduced the number of pregnant ewes available for allocation to each treatment and in order to maintain adequate animal numbers per treatment, one of the originally designed treatments (ad-libitum feeding from day 50 to day 140 of pregnancy) had to be removed from the experiment. The reason for the low conception rate could not be attributed to any known factors (sire, source of ewes, AI technician, day of AI, nutritional treatment.) and remains unknown. Whatever the reason (or reasons) for this low conception rate, having to remove a treatment from the experimental design somewhat limited the comparisons possible and the conclusions drawn.

A second limitation of this experiment was the necessity to manage the ewes in two groups, those offered PM and those offered AL levels of feeding at any given time, irrespective of their ultimate nutritional combination treatment. Rather than managing five individual treatment mobs, ewes were moved between either PM or AL paddock areas depending on what their treatment required them to be offered. This was done for practical reasons so that

two separate farm areas could be managed to obtain the target pasture allowances. This also decreased potential confounding between-paddock differences across the treatments. Pasture allowances in the PM paddock areas were designed to ensure that ewes in the control treatment were indeed fed at or very close to their pregnancy maintenance requirements, thereby maintaining the efficacy of the control group. However, ewes that were previously AL-fed lost weight when returned to the PM paddock areas suggesting that they were not fed at their estimated pregnancy maintenance requirements. Whilst this was a limitation because any potential positive effect of AL-feeding could have been obscured by the mild undernutrition in the subsequent period, it helped to clarify why AL-feeding should not be used as a managerial tool to increase lamb birth weight. It was discussed that providing ewes with AL-feeding at any stage of pregnancy increases their LW and BCS. These heavier ewes may have an increased feed demand relative to lighter ewes for the subsequent period post AL feeding.

6.5 Practical implications for sheep grazing systems

The results from this thesis highlight the importance of monitoring ewe nutrition during pregnancy to achieve optimum lamb BW and WW. In order to better manage ewe nutrition during pregnancy, farmers should make use of available technologies such as pregnancy scanning, body condition scoring, assessment of pasture mass and feed budgeting. Body condition score at mating is perhaps the most important managerial target to achieve and is currently recommended to be around 3 and 3.5 (Kenyon et al. 2014). If this level is successfully achieved, the nutrition during the first 100 days becomes relatively simple because ewe BCS and/or LW should be managed so as to be maintained (i.e. BCS) or increased with the expected conceptus mass at any given time point (i.e. LW) during this

period. In practice, however, this target is often not met, at least by a proportion of the flock. Thus, LW and BCS gains are often required in early-mid pregnancy to make up for this short-fall. In preparation for winter, and prior to pregnancy scanning, farmers should target ewes in a poor nutritional status (usually recognised on-farm as being in poor body condition) to achieve adequate body reserves before day 100 of pregnancy. If an apparent feed shortage is envisioned, prioritising the best feed on-farm to ewes in poor BCS, whilst keeping the rest of the flock at maintenance is essential to achieving these targets over the whole flock.

Understanding how much feed and herbage growth is available on-farm is essential during winter. In the absence of enough pasture to adequately feed ewes, reducing the number of animals on-farm or buying in additional feed are options to ensure adequate nutrition of pregnant ewes. However, this study suggests that ewes can tolerate short to moderate periods of undernutrition of between 30 and 50 days, depending on the severity of undernutrition, with only limited and perhaps no effects on the lamb if the nutrition of the ewe is restored later in pregnancy. Longer periods of undernutrition of 70 to 90 days during early-to-mid pregnancy should be avoided since they can have permanent small to moderate size effects on lamb BW that can be carried through to weaning, even when nutrition is adequate during late-pregnancy and lactation. Ewe BCS losses of 0.5 to 1 units have been suggested (Russel 1984a, 1984b) to be acceptable, with minimal impacts on productivity (Kenyon et al. 2014). During the first 100 days of pregnancy, pregnancy scanning is perhaps the best available tool that farmers have available to make use of the differences in nutrient requirements between singleton- and twin-bearing ewes to best manage pasture allocation. The present study suggested that singleton-bearing ewes may

better cope with a nutritional restriction during early-to-mid-pregnancy and any effects on the singleton lamb is less detrimental to its survival, than the effect on a smaller, lighter, twin.

Limiting the intake of the late-pregnant ewes will result in a decrease in lamb BW and WW. The results from this study suggest that ewes that have previously experienced a nutritional stress and those bearing multiples are likely to be at a greater risk than singleton-bearing ewes and those with optimal body reserves on day 100 of pregnancy. Thus, farmers should aim to maintain the BCS of the latter ewes and provide those in the former with sufficient feed to either increase or maintain BCS, respectively. Kenyon et al. (2014) suggested a minimum BCS at lambing of 2.0 to minimise any potential BCS loss during lactation.

6.6 Future research consideration

6.6.1 A meta-analysis guide for animal scientists

Basic animal research generates results that have a low aggregation level such that results are specific to the study, and thus the need to quantitatively integrate this research evidence using meta-analysis (St. Pierre, 2007). Knowledge about meta-analysis not only enables scientist to evaluate and interpret meta-analytic results, but also allows them to consider their research and the way it is published so it can contribute to the larger picture within a research topic (Gerstner et al. 2107). Perhaps the major future endeavour arising from this thesis is the development of a meta-analysis guide for animal scientists. Currently only one publication deals with this topic (Lean et al. 2009), however, the methods presented are outdated and much of the progress in meta-analytic tools (presented in this study) requires further explanation.

The present work shows that primary research related to the effect of ewe nutrition during pregnancy on fetal/lamb weight requires higher publication standards since only between 15% and 40% of the available evidence can currently be used for meta-analytic purposes. Data from these experiments vary in the populations used, geographical locations, the basal plane of nutrition, nutrition post-treatment, study design and many other study, maternal and offspring related factors. Meta-analysis can assess the contribution of these factors to the variation in study results, but integration of results is often hindered by poor or inadequate description of study designs, missing information and traceability of experiments and the inadequate details when reporting outcomes. Reporting usable outcomes to calculate effect sizes is therefore essential in primary research to assist later meta-analytic review. Meta-analytic thinking can therefore facilitate the future integration of results, leading to a better interpretation and understanding of a research topic.

6.6.2 Better and larger early- and mid-pregnancy undernutrition studies

Research has largely focused on late-pregnancy maternal nutrition given its known effect on offspring growth and development. Grazing and indoor experiments have shown consistent results whereby exposure to periods of late pregnancy undernutrition negatively affect both the ewe and the lamb. On the contrary, results from studies examining early- and mid-pregnancy undernutrition are mixed, with both positive and negative effects being found. Grazing experiments examining early pregnancy nutrition have been particularly scarce and many of the available studies suitable for use in meta-analysis are based on small numbers of animals. It could be argued that small studies have more “internal validity” than larger studies, that is, their results may more closely resemble the effect

measured, given the tightly controlled nature of these studies (Lean et al. 2009). However, and in contrast to large studies, results from these small studies cannot be extrapolated to commercial scale populations, meaning that they have less external validity. The advantage of using meta-analysis to combine these studies is that the combined findings should have a higher external validity than any single study (Lean et al. 2009). However, as stated earlier, no single study, whether this is meta-analytic or simply experimental, can give a definitive answer about a particular treatment, unless the available evidence is of high and reliable quality. In order to validate current evidence, future research in the area of early- and mid-pregnancy undernutrition will need to be conducted using larger numbers of animals, possibly on a farm scale, in order to detect the potentially subtle impacts on LGFW, BW and WW. Ideally this research needs to not only focus on the effects of varying levels of maternal nutrition on the offspring, but also on how the ewe responds to nutritional challenges.

6.6.3 Can results from periconceptional undernutrition studies be replicated using farm-scale research?

The validity of PCUN studies has been questioned for agricultural purposes, since it is not common practice to restrict the intake of ewes prior to or during the breeding season due to potential impacts on ovulation and conception rates (Symonds et al. 2010). In practice, however, this scenario is possible in at least a proportion of the flock or under dry weather conditions that can negatively affect feed supply. The current evidence from PCUN studies presented in this thesis was based on results from studies coming from one research group (as studies from other research groups did not meet inclusion criteria) and that had limited sample sizes. Results from PCUN experiments have shown an increase in birth weight of

singleton lambs between 0.5 and 1.4 kg but had little effect on twin lambs (Jaquiere et al. 2011, 2012), with other metabolic and neurodevelopmental consequences observed later in life (Rae et al. 2001; Lie et al. 2013; Zhang et al. 2013; see also the review by Bloomfield, 2011). Again, most studies are somewhat underpowered and whether PCNU and its associated effect on the ewe and her lambs can affect other important production parameters like conception rates, ovulation rates, lambing rates and survival has not been reported, although studies focused on undernutrition and ovulation rates only, clearly show it does (Kenyon and Webby, 2007). Experimental replication with emphasis on farm-scale experiments is therefore needed to validate these results.

6.6.4 Is the magnitude of the effect of undernutrition similar for singletons and twins relative to their potential size and can this be extended to triplets?

The present study demonstrated, somewhat surprisingly, that there was no significant difference in the magnitude of the effect of maternal undernutrition for singletons and twins and evidence from one large scale experiment confirms this result. There is great potential in considering this premise in future experiments for two reasons. Firstly, it is desirable to determine if the growth of lambs from birth to weaning is also equally sensitive to maternal undernutrition during pregnancy regardless of litter size. Secondly, the is value in understanding whether this premise can be extended to include lambs born as triplets. A 2 x 2 or 3 x 2 factorial designs including singleton, twins and triples and two levels of nutrition (pregnancy maintenance vs undernutrition) may help understanding whether the marginal effect of undernutrition is similar across litter types. This may also change the way nutritional studies are published, leading to more usable information for future meta-analyses.

6.7 Concluding remarks

The present study represents the first meta-analytic approach examining the effect of changes in the ewe nutrition during pregnancy on the growth of their offspring at various developmental stages. This study showed that late-pregnancy undernutrition should be avoided as it is associated with a decrease in fetal weight in late-gestation, birth weight and weaning weight. In the whole flock, multiple bearing ewes and ewes with poor body reserves 6 to 8 weeks prior to lambing, such as those experiencing long-term undernutrition periods, are at a greater risk relative to singleton bearing ewes and ewes that have not previously experienced a period of undernutrition. It was also shown that early- and mid-pregnancy undernutrition have little to no effect on LGFW, BW and WW when nutrition during late-pregnancy is sufficient to meet or surpass the ewe pregnancy requirements; and even when severe undernutrition is employed for experimentation, effects are small in magnitude. Thus, demonstrating that the effects of poor nutrition in early- and mid-pregnancy can, in most cases, be overcome by providing ewes with adequate nutrition during late-pregnancy and lactation. However, large-scale experiments may be needed to detect the potentially subtle effects on the ewe and her lambs along with other production effects. Furthermore, very few experiments have considered the effect of above pregnancy maintenance feeding on LGFW, BW and WW, with fetal and lamb weight responses that vary greatly across experiment. In the absence of enough information related to the effect of above pregnancy maintenance feeding at each stage of pregnancy, meta-analyses were unable to identify possible differential effects across stages and/or with increasing length of manipulation. Therefore, a field experiment was designed to address this gap in the knowledge by providing twin-bearing ewes with *ad-libitum* feeding at various stages of

pregnancy and for differing lengths of time. Relative to a control groups of ewes fed to meet their PM requirements, *ad-libitum* feeding was successful in increasing ewe LW and BCS, for at least the period of manipulation, but failed to increase lamb BW and WW. Further evidence suggested that *ad-libitum* feeding during late-pregnancy may negatively affect lamb survival. Therefore, ad-libitum feeding offers no advantage as a management tool to increase lamb BW and WW in twin bearing ewes when nutrition during lactation is non-limiting. However, further work needs to consider the effects when nutrition in lactation is insufficient to meet the ewe requirements before final conclusions can be made.

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