Meta-analysis of lamb birth weight as influenced by pregnancy nutrition of multiparous ewes

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ABSTRACT: Across the literature, there is large variation in lamb birth weight responses to changes in the ewe pregnancy nutrition. Much of this heterogeneity has been attributed to several factors inherent to each experiment; however, the relative contribution of these experimental factors has not yet been quantified. This meta-analysis aimed to systematically review the variation in lamb birth weight responses across nutritional studies involving adult multiparous ewes. Effect-sizes for individual studies were estimated using the unbiased estimator Hedges' g , whereby positive and negative values indicate heavier and lighter treatment lambs vs. controls, respectively. Heterogeneity varied between early-, mid- and late-pregnancy undernutrition studies ($I^2_{\text{total [early pregnancy]}} = 19.90\%$, $I^2_{\text{total [midpregnancy]}} = 52.10\%$, $I^2_{\text{total [late pregnancy]}} = 68.70\%$).

The small average effects for early- (0.04, highest posterior density [HPD] interval = -0.22, 0.28) and mid-pregnancy undernutrition (-0.15, HPD interval = -0.35, 0.05) suggest that if farmers anticipate a potential feed shortage, ewes can be allowed to lose weight providing 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 (-0.72, HPD interval = -0.86, -0.55). Thus, management practices should focus on ensuring adequate nutrition in late pregnancy. Increasing lamb birth weight could be possible by feeding ewes above their pregnancy maintenance requirement (0.23, HPD interval = 0.002, 0.48), though the number of studies is limited and further research is needed.

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

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J. Anim. Sci. 2018.96:1962–1977

doi: 10.1093/jas/sky072

INTRODUCTION

There is strong evidence indicating that the nutrition of the pregnant ewe plays a key role in determining the weight of a lamb at birth, which in turn is a predictor of lamb mortality (Fogarty et al., 2000). A number of traditional (Harding, 2001; Rhind et al., 2001, 2003; Greenwood and

Bell, 2003; Rhind, 2004; McMillen and Robinson, 2005; Bell, 2006; Wu et al., 2006; Caton and Hess, 2010; Kenyon and Blair, 2014) and systematic (Rooke et al., 2015) reviews have reported that late-pregnancy maternal undernutrition can reduce lamb birth weight. Whereas, early- and mid-pregnancy undernutrition (Greenwood and Bell, 2003; Gardner et al., 2007) and overnutrition of mature ewes (Kenyon and Blair, 2014; Bell and Greenwood, 2016) were found to have only a small impact. From an agricultural perspective, however, the picture may be less clear because individual studies have been undertaken under a large array of

¹F.J.R.F. was funded by Gravida, National Centre for Growth and Development.

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Received December 18, 2017.

Accepted February 26, 2018.

experimental conditions. This has resulted in large differences in estimated effects, which can be attributed to 3 groups of factors: first, study-related factors, which include the type, timing, length of time, and severity of the nutritional manipulation; second, maternally related factors, which include breed, age, body weight, and body condition; and third, offspring-related factors, which include gestation length, genotype, litter size, and sex (Harding and Johnston, 1995; Luther et al., 2005; Kenyon and Blair, 2014; Bell and Greenwood, 2016). To date, however, the contribution of these groups of factors to the variability in study results has not yet been quantified. Quantitative synthesis, also known as meta-analysis, can be employed to extend current knowledge. The objectives of the present study were first to use a meta-analytic approach to estimate the overall effect of changes in the ewe nutrition during pregnancy on lamb birth weight; second, to quantify the contribution of various factors that may be driving the variability in study results; and third, to consider the biological relevance of the combined effects from an agricultural perspective. Two hypotheses were tested: first, that undernutrition would have an increasing detrimental effect on lamb birth weight as pregnancy progresses and second, that maternal nutrition above the theoretical requirements for pregnancy would have no effect on lamb birth weight.

MATERIALS AND METHODS

Currently, many reporting guidelines exist for the publication of systematic reviews and meta-analyses in the Health and Social Sciences. However, no such guidelines currently exist for publication of meta-analyses in the Animal Sciences. For this reason, the present study is structured, as closely as possible, according to 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 (see [Supplementary Material](#) for the checklist in this study) describing the main information that needs to be specified in a meta-analysis. In addition, a 4-phase flow diagram is available that allows visual assessment of the processes undertaken from literature search to final inclusion/exclusion decisions (see also [Fig. 1](#)).

Literature Search

Our systematic review and meta-analysis targeted experimental studies involving nutritional manipulations in sheep, above and/or below the theoretical requirements for pregnancy. The initial

literature search was conducted in 3 online databases (PubMed, SCOPUS, and Web of Knowledge) to identify studies published up to July 22, 2014 without publication date and language restrictions. The following Boolean search was adapted to suit the 3 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*). All the retrieved records were screened to find potentially relevant studies and key reviews. These relevant studies and key reviews 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 database search. This literature search process yielded 4,872 records after duplicates were removed ([Fig. 1](#)). These records were screened for suitability based on their title, abstract, full text, supplementary materials, and information obtained directly from the authors.

Study Selection Criteria and Relevance Screening

Potentially relevant studies were included in our analysis only if they satisfied the following pre-specified 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 (periconceptional and flushing periods included);
- 4) outside the treatment periods, ewes had to be fed at their theoretical requirements for pregnancy or above.
- 5) studies must provide birth weight data for naturally-born lambs for both control and treatment groups;
- 6) birth weight statistics had to be reported for each individual birth type; and
- 7) had sufficient information to calculate an effect-size between a control and a nutritionally manipulated group. The information required to calculate an effect-size included: the number of lambs in each treatment, the mean birth weight for each treatment and their corresponding

Figure 1. 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.) is given for each dataset.

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, adolescent (7 to 10 mo of age at breeding), or nulliparous (first lambing regardless of age) sheep were also excluded. Last, 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.

The main data for this study were extracted from information presented in tables, figures, and text. GraphClick (Arizona-Software, Los Angeles, CA; 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. If adequate clarification or data could not be provided, the study was excluded.

Data Coding and Datasets

Extracted data from the selected studies were 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 females independently within the same study ($n = 9$), these data were pooled. An additional identifier variable (control group ID) was coded to account for potential correlated structures within the data because 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 (indoors or outdoors); 2) litter size (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), 6) day of pregnancy when the nutritional manipulation finished (end day), and 7) lamb genotype (purebred or crossbred). To be able to use lamb genotype in our analysis, some assumptions had to be made or studies had to be removed. For example, where the maternal breed was recorded as purebred or crossbred but ram information was not available, the resulting lambs were assumed purebreds or crossbreds, respectively. In addition, limiting our analyses to only studies in which we can distinguish between purebred and crossbred lambs would mean to limit the scope of the review itself, as it would require the removal of a large amount of information. Therefore, given the lack of significance of lamb genotype in our exploratory model, it was removed from further investigation.

An additional predictor was created by categorizing studies within each stage of pregnancy. Early pregnancy included all studies with nutritional manipulation starting prior to mating (day 0) until day 35 of pregnancy. Midpregnancy included 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, independent of the start day. Last, the level of feeding of the control group was coded as either pregnancy maintenance (PM) or above PM (well fed [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 BW data provided in the manuscript, if available.

In the present study, the term “pregnancy maintenance requirements” is defined as the amount of energy required to maintain ewe net BW

throughout pregnancy, while 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 setups found in the literature, 2 main datasets were generated:

- 1) Undernutrition (UN) dataset: the extracted data involved the comparison between a control-fed group and experimental ewes fed below PM requirements.
- 2) Overnutrition (ON) dataset: this dataset 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).

Effect-Size Calculation

To quantify the birth weight responses to maternal nutrition, Hedges’ g (Hedges, 1981; hereafter g) was used as the effect-size metric for this study. Hedges’ g in the present study represents the standardized mean difference in birth weight between the experimental group and the control group in terms of the pooled SD, with a correction for small sample sizes (Hedges, 1981). 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’s (1988) interpretative guidelines, where the magnitude of an effect can be classified as small ($g = 0.2$), moderate ($g = 0.5$), or large ($g = 0.8$).

Statistical Analysis

All statistical analyses were performed using R v.3.0.2 (R Development Core Team, 2013). The 2 main datasets were analyzed 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).

Meta-analysis

Traditional random-effects meta-analysis (model I, Nakagawa et al., 2017) was used to estimate the mean effect and the amount of variation across

studies based on all effect-sizes. 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](#)):

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

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

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

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

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

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 ($j = 1, \dots, N_{\text{experiment}}$) applied to the i th effect-size ($i = 1, \dots, N_{\text{effect-size}}$; $N_{\text{effect-size}}$ is the number of effect-sizes), $\mathbf{s}$ is a 1 by $N_{\text{experiment}}$ 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 $N_{\text{experiment}}$ vector of 0 and $\mathbf{I}$ is the $N_{\text{experiment}}$ by $N_{\text{experiment}}$ identity matrix; $b_{k[i]}$ (only used in the undernutrition meta-analysis) is the breed-specific effect for the k th breed ($k = 1, \dots, N_{\text{breed}}$; 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 $N_{\text{experiment}}$ 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 $N_{\text{experiment}}$ 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 $N_{\text{experiment}}$ by $N_{\text{experiment}}$ matrix, with its diagonal elements being σ_m^2 , which is assumed to be known.

Meta-regression

Meta-regressions (model II) were constructed as mixed models that incorporated the following potential predictor variables: 1) level of nutrition of the control group (PM vs. WF; undernutrition dataset only), 2) litter size, 3) total days, 4) start day,

5) end day, 6) year of publication, and 7) 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, $\beta_{1..n}$ are regression coefficients and represent the change in effect-size for unit increase in x , with $x_{1..n}$ 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 (i.e., they had a mean of 0 and SD of 1). Their regression coefficients can, therefore, be interpreted as the amount of change in effect-size when the predictor value changes by 1 SD.

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*: $V = 1$, $\text{nu} = 0.002$, $\alpha.\mu = 0$, $\alpha.V = 1,000$), while we used the default prior (a diffused noninformative prior) for fixed effects. Model convergence and mixing were accessed 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 ([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, SD, and 95% highest posterior density (HPD) intervals was collected for 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.

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 follows:

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

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:

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

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

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

where σ_{exp}^2 is the experiment-level variance, σ_{breed}^2 is the dam breed-level variance, and 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 $\sigma_{\text{exp}}^2 / \sigma_t^2$ and is $\sigma_{\text{breed}}^2 / \sigma_t^2$, respectively.

R² 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 ($R^2_{\text{LMM}(m)}$) measures the variance explained by the fixed effects as a proportion of the sum of all variance components, whereas the conditional R^2 ($R^2_{\text{LMM}(c)}$) determines the variance explained by both fixed and random factors.

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 nonstatistically 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 nonindependent 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).

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 5 lambs or less (in either the control or treatments groups) 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 Tweedie, 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 of this study.

RESULTS

Study Retrieval and Selection Strategy

The course of the systematic review in the present study is illustrated in the 4-phase flow diagram following the PRISMA statement (Fig. 1). After filtering all relevant information, 70 suitable studies were included in the dataset representing 2 major experimental setups: relative undernutrition ($n = 61$) and overnutrition ($n = 15$). Some studies reported on experiments undertaken in both experimental setups (undernutrition and overnutrition). The 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.

Study Characteristics and Meta-analysis: Undernutrition

The undernutrition dataset consisted of 61 primary studies involving 68 different experiments (Supplementary Table S1). A total of 132 observations were extracted from these primary studies and were used for analysis. The experiments included for analysis had been conducted across a time span of 66 yr, dispersed across years as follows: 9% before the 1970s, 32% between 1970 and 1990, 7.5% between 1991 and 2000, 23% between 2001 and 2007; and 28% between 2008 and 2014. Although no single author or set of authors dominated by contributions to the dataset (the most being 13% for a single researcher; Holst et al., 1986), 80% of observations originated from 3 locations: Australia (28%), New Zealand (19%), and the United Kingdom (33%). The remainder of the data were distributed among 11 countries.

There was insufficient number of studies reporting the energetic level during the period of restriction and/or data related to the effect of the undernutrition regimens on the ewe BW or their body condition score (BCS). Often, ewe BW data were either not reported, reported without a measurement of dispersion, presented in illegible graphs

(e.g., error bars overlapping across treatments), or were not comparable across experiments (e.g., BW change vs. BW from mating to lambing vs. BW at start of restriction to postlambing). Within the early-, mid- and late-pregnancy studies, only 4, 3, and 15 studies, respectively, had ewe BW data suitable for meta-analysis. This represents only 25% 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). Thus, it was not possible to investigate how changes in the level of undernutrition or changes in ewe BW and BCS influenced lamb birth weight responses across experiments.

Over all the experiments analyzed, maternal undernutrition during pregnancy resulted in lambs that were half an SD ($g = -0.52$) lighter than their control counterparts (Table 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. A preliminary meta-regression model (Table 1: Meta-regression model 1) included predictors for litter size, timing of undernutrition (the day when the nutritional restriction started), the length of

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

Models of the undernutrition dataset			
Description	Meta-regression		
	Meta-analytic model	Model 1	Model 2
Fixed effects	β [95% HPD]	β [95% HPD]	β [95% HPD]
Intercept	-0.52 [-0.73, -0.33]	0.55 [-0.74, -0.37]	—
Litter size	—	0.02 [-0.22, 0.28]	—
Start day	—	0.30 [-0.43, -0.19]	—
Total days	—	0.15 [-0.26, -0.05]	—
Publication year	—	0.20 [0.07, 0.35]	—
Early pregnancy	—	—	0.04 [-0.22, 0.28]
Midpregnancy	—	—	-0.15 [-0.35, 0.05]
Late pregnancy	—	—	-0.72 [-0.86, -0.55]
Random effects	VC	VC	VC
Experiment	0.068	0.022	0.024
Breed	0.100	0.063	0.046
Residual	0.133	0.086	0.069
PCV _[Experiment]	—	68%	65%
PCV _[Breed]	—	37%	54%
PCV _[Residual]	—	35%	48%
I^2_{total}	76.30	—	—
$R^2_{\text{LMM}(m)}$	—	47.30%	41.03%
$R^2_{\text{LMM}(c)}$	—	73.36%	70.65%
DIC	172.21	120.38	93.29

95% HPD intervals excluding zero can be considered statistically significant (bold font). DIC = deviance information criterion; HPD = highest posterior density; PCV = proportion change in variance; VC = variance components.

time of undernutrition, and publication year (as a binary variable where 1 is studies published after the 1990s and -1 those published before the 1990s). Given the scaled moderators fitted in the model, the overall intercept (Table 1: Meta-regression model 1) is based on studies in twins that were published after the 1990s at the average values ($\pm$ SD) for start day (59.56 ± 48.99) and total days of manipulation (57.89 ± 29.55). Among all these predictors, the “timing of nutritional manipulation,” the length of time of undernutrition, and the publication year significantly influenced the degree to which birth weight was affected, with the timing of undernutrition having the largest influence on experimental outcomes. However, there was no significant effect of litter size, which represents the difference in effect-size magnitude between studies in singletons and twins.

On the basis of these results, studies were categorized by the time in pregnancy they were undertaken (early pregnancy, midpregnancy, or late pregnancy) and this categorical predictor was fitted in a meta-regression model (Table 1: Meta-regression model 2). Overall, undernutrition in early pregnancy and midpregnancy had no significant effect on lamb birth weight, whereas maternal undernutrition during or extending into late pregnancy resulted in a significant decrease in lamb birth weight. This single-predictor meta-regression model was able to explain over 70% of the variation in the data (only 3% less than the meta-regression with 4 predictors) and reduced both the experiment and residual-level variances by 65% and 48%, respectively, relative to the meta-analytic model. Finally, 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 thus, it was omitted from further analyses.

Additional subgroup analyses were conducted to uncover potential sources of variation within studies undertaken at each stage of pregnancy. Results from these subgroup analyses not only confirmed the marked differences in birth weight responses to undernutrition at different stages of pregnancy (Supplementary Figs S1–S3) but also revealed varying levels of heterogeneity in each subgroup ($I^2_{\text{total [early pregnancy]}} = 19.90\%$, $I^2_{\text{total [midpregnancy]}} = 52.10\%$, $I^2_{\text{total [late pregnancy]}} = 68.70\%$). There were a limited number of studies undertaken in early pregnancy and midpregnancy that were suitable for meta-analysis, and no individual predictor or group of predictors helped to further explain the heterogeneity in these subgroups. Most of the

heterogeneity in these subgroups remained at the residual and experiment levels for early-pregnancy ($I^2_{\text{residual [early pregnancy]}} = 70\%$) and mid-pregnancy studies ($I^2_{\text{experiment [midpregnancy]}} = 85\%$), respectively. That is, much of the variation among effect-sizes in the early-pregnancy subgroup remained unaccounted for in this meta-analysis. On the contrary, the within-study variation (i.e., I^2_{residual}) in the mid-pregnancy subgroup was small, leaving a large amount of variation attributable to study-specific factors (e.g., most likely differences in study design).

The late-pregnancy subgroup included 2 types of experimental designs: 1) late-pregnancy undernutrition only (i.e., from day 90 to term) or 2) long-term undernutrition that extended into late pregnancy. Only a few outdoor experiments were usable for meta-analysis, with the majority of studies in this subgroup being undertaken indoors (see Supplementary Table S1). Similarly to the main analysis, late-pregnancy undernutrition was associated with a significant decrease in lamb birth weight ($\beta_{\text{[meta-analytic mean]}} = -0.75$, 95% HPD = -0.92 to -0.60). Indoor experiments observed significantly larger effects on birth weight ($\beta_{\text{[indoors]}} = -0.85$, 95% HPD = -1.02 to -0.68) than outdoor experiments ($\beta_{\text{[outdoors]}} = -0.55$, 95% HPD = -0.82 to -0.34). In addition, a significant publication year effect was found ($\beta_{\text{[publication year]}} = 0.24\%$ 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 in this data subset.

Study Characteristics and Meta-analysis: Overnutrition

Only 15 overnutrition studies were deemed acceptable for quantitative analysis (Table 2). A total of 25 observations were extracted from these studies, which were conducted across a time span of 43 yr. The extracted data was representative of variations in the duration of overnutrition rather than overnutrition at specific stages of pregnancy. 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 and significant increase in lamb birth weight (Table 3; Fig. 2) when compared to PM-fed ewes. Large heterogeneity across

Table 2. Summary of papers used for meta-analysis in the overnutrition dataset

First author, year	Ewe breed	Overnutrition level/body weight change [‡]	Period of overnutrition [§]	Lamb genotype*	Litter size and difference in lamb birth weight relative to control (g)
Long, 2011	Rambouillet × Columbia	1.5PM – ↑~34.6 kg	–60 to 150	CB	Singles – Male + Female = +800
Ford, 2009	Rambouillet × Columbia	1.5PM – ↑~27 kg	–60 to 148	CB ¹	Singles – Male + Female = +970
Zhu, 2009	Rambouillet × Columbia		–60 to 148	CB ¹	Twins – Male + Female = +680
Kenyon, 2011	Romney	↑~3.8 kg	21 to 49	PB	Twins – Male + Female = –90
Kenyon, 2009	Romney	Single – ↑~0.5 kg ^{MT} Twin – ↑~1 kg ^{MT}	21 to 140	CB	Singles – Male + Female = +160 Twins – Male + Female = +710
Kenyon, 2011	Romney	↑~5.2 kg	21 to 140	PB	Twins – Male + Female = –337
Kenyon, 2011	Romney	↑~4.4 kg	50 to 139	PB	Twins – Male + Female = –274
Morris, 2004	Romney	6 cm – ↓0.5 kg ^{CF} 8 cm – ↓0.7 kg ^{CF}	64 to 147	PB	Twins – 6 cm – Male + Female = +209 Twins – 8cm – Male + Female = +295
Hashemi, 2008	Karakul	1.1PM – ↑0.8 kg ^{CF}	90 to 150	PB	Singles – Male + Female = –260
Khalaf, 1979	Border-Leicester × Cheviot	Single – ↑13.7 kg ^{MT} Twin – ↑~5.2 kg ^{MT}	90 to 150	CB ¹	Singles – Male + Female = –120 Twins – Male + Female = +580
Banchero, 2004	Merino	NE	134 to 149	PB	Twins – Cracked maize – Male + Female = +500
Hawken, 2012	Merino	NE	134 to 148	NA ²	Twins – Calm – Male + Female = +185 Twins – Nervous – Male + Female = +830
Kenyon, 2012	Romney	BCS2 – ↑3.3 kg BCS2.5 – ↑1.6 kg BCS3 – ↑~3 kg	112 to 136	PB	Twins – CS2 – Male + Female = –200 Twins – CS2.5 – Male + Female = –100 Twins – CS3 – Male + Female = +200
Economides, 1981	Chios	Singles – ↑1.3 kg Twins – ↑2.2 kg	107 to 152	NA	Singles – Male + Female = –220 Twins – Male + Female = +330
Khanal, 2014	Texel crossbred	1.5PM – ↑~4.1 kg	105 to 147	CB ¹	Twins – Male + Female = +30
Treacher, 1971	Dorset Horn	Single – ↑8.8 kg Twin – ↑6 kg	105 to 147	NA	Singles – Male + Female = +130 Twins – Male + Female = +360

In some papers, more than one effect-size was obtained and is repeated throughout the table.

[‡]The level of overnutrition (i.e., relative to pregnancy maintenance [PM]; as pasture height; or as ewe body condition score [BCS]) is shown when and as stated by the authors. Body weight change was calculated as the difference in BW gain/loss between the control and overfed groups between the start and end of the nutritional treatment, including conceptus mass. In studies marked with “CF”, BW change was calculated as the difference in ewe BW between the start of the nutritional treatment and the postlambling weight. In studies marked with “MT”, BW change was calculated as the difference between mating weight and postlambling weight.

[†]NE = non-estimable from the provided information.

[§]Days of pregnancy, where 0 (conception) and 150 (approximate term).

*PB = Purebred; CB = Crossbred; NA = not available information.

¹No ram information was available but assumed to be crossbred.

²No ram information was available.

results was observed ($I^2_{\text{total}} = 74.80\%$), and given the few observations available, no individual predictor tested was able to further explain the residual heterogeneity. Nevertheless, Fig. 3 illustrates the difference in effect-sizes across studies undertaken indoors and outdoors plotted against their precision. Two points are clear from Fig. 3: first, that outdoor experiments were undertaken with larger sample sizes than indoor experiments and second, that responses were more variable in outdoor relative to indoor experiments, where the majority of studies have found positive effects on lamb birth weight. Indeed, the meta-regression analysis (Table 3) suggested that, overall, indoor experiments observed a significant increase in lamb birth weight, while outdoor experiments resulted in a nonsignificant intercept.

Publication Bias

Visual inspection of funnel plots in the under-nutrition dataset (Fig. 4a and b) 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 of studies at each stage of pregnancy revealed a significant Egger’s regression intercept only for the late-pregnancy studies (Fig. 4a and b; red dots; $\beta_{[\text{intercept} - \text{Late}]} = -1.59$, 95% HPD = -2.45 to -0.86). On the contrary, the nonsignificant intercept of Egger’s regression in the overnutrition dataset indicated little evidence of publication bias ($\beta_{[\text{intercept}]} = 0.09$, 95% HPD = -1.77 to 2.01 ; Fig. 4c and d).

Table 3. Summary of the statistical results of meta-analytic and meta-regression models in the overnutrition dataset

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%
P^2_{total}	74.80%	–
$R^2_{\text{LMM}(m)}$	–	11.60%
$R^2_{\text{LMM}(c)}$	–	66.73%
DIC	5.96	7.13

95% HPD intervals excluding zero can be considered statistically significant (marked in bold font). DIC = deviance information criterion; HPD = highest posterior density; PCV = proportion change in variance; VC = variance components.

Sensitivity Analysis

Two studies were removed for sensitivity analyses: [Holst et al. \(1986\)](#) were excluded from analysis because it introduced a significant amount of non-independence as it contributed 13% of the effect-sizes in the undernutrition dataset. [Wallace \(1948\)](#) was 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 ([Nordby et al., 1986](#)—Twin data; [Krausgrill et al., 1999](#)—Experiment 2; [Gardner et al., 2005](#); [Hyatt et al., 2007](#)).

Results from the sensitivity analysis are shown in [Supplementary Table S2](#). Removing the 25 observations did not influence the pattern of results presented in the main analyses. For example, overall effects were similar to those in the main analysis for early-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = 0.05$, 95% HPD = –0.19 to 0.28), mid-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = -0.21$, 95% HPD = –0.43 to 0.01), and late-pregnancy undernutrition ($\beta_{[\text{meta-analytic mean}]} = -0.69$, 95% HPD = –0.83 to –0.54).

Further exploration for publication bias in the late-pregnancy studies indicated a significant intercept of Egger's regression on the residuals and measurement 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. The trim-and-fill analysis of the main results suggested 8 studies missing from the bottom left of the plot (i.e., low sample size studies observing a large increase in birth weight as a result of maternal undernutrition in late pregnancy). It is possible that small, late-pregnancy undernutrition studies showing positive effects on lamb birth weight are missing. Alternatively, and given the moderate estimated heterogeneity in the data 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 attributed to between-study variation (i.e., heterogeneity) rather than true publication bias.

DISCUSSION

This meta-analysis sought to systematically review the variation in birth weight responses to maternal nutrition during pregnancy and to determine the implication this may have for sheep production systems. We 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 a decrease of up to 22% in lamb birth weight. On the contrary, early- and mid-pregnancy undernutrition had little impact on lamb birth weight when nutrition was re-established to adequate levels after the period of restriction. Overall, the results of this meta-analysis 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](#)), a systematic review ([Rooke et al., 2015](#)), and a previous meta-analysis of late gestation fetal weight ([Gootwine, 2013](#)). 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 number of relevant studies available for meta-analysis suggests only a small effect that may not justify any practical application for livestock production, especially for grazing systems, but more experimental studies are needed before firm conclusions can be drawn.

We observed no overall evidence of a major effect of early- and mid-pregnancy undernutrition

Figure 2. Forest plot of the overall effect (mean and 95% high posterior density interval) of overnutrition on lamb birth weight. Effect-sizes from individual studies are represented by triangles, and estimated SE are represented by whiskers.

Figure 3. Funnel plot of effect-sizes in the overnutrition dataset plotted against their precision (1/SE). Red and gray bubbles are effect-sizes for studies undertaken indoors and outdoors, respectively. Differences in bubble circumference accentuate the differences in sample size between studies.

on lamb birth weight. Re-establishing the ewe’s feeding levels to PM or above, 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 our meta-analysis, studies were selected so that maternal nutrition post-treatment was resumed to either

Figure 4. 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 pregnancy, midpregnancy, and late pregnancy.

PM or above, thereby our results are in line with this suggestion. Unfortunately, information on the level of undernutrition (in the form of ewe BW and BCS loss) was difficult to obtain from the published studies. Therefore, we were not able to analytically resolve the extent of BW or BCS loss that ewes can endure before measurable effects are seen on lamb birth weight.

In the early-pregnancy undernutrition studies included in this meta-analysis, maternal BW data were not reported in 4 studies. In addition, 2 studies in which “severe” undernutrition (50% PM) was used had no effect on ewe BW during the restriction period (Chadio et al., 2007; 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 BW 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 BW loss between experiments and its effect on the ewe’s body reserves at mating. A steady decrease in ewe BW throughout the restriction period (e.g., Debus et al., 2012) or a minor decrease in ewe BW (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 BW (~8 kg; Oliver et al., 2005). This decrease in BW, 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 BW and BCS compared to controls. The effect of such a level of undernutrition was still apparent close to lambing with restricted ewes being ~6 kg lighter than controls. Again, it is difficult to draw conclusions from studies where maternal data were not reported (Hernandez et al., 2009; Jaquiere et al., 2011, 2012), especially because these results appear to contradict those of Oliver et al. (2005) and, more interestingly, reported different effects on singletons and twins.

No particular pattern in birth weight responses to mid-pregnancy undernutrition arises from the included studies, which was reflected in the large proportion of heterogeneity remaining at the experiment level. Observations on the effect of mid-pregnancy undernutrition on placental weight (Luther et al., 2005) and late gestation fetal weight (Gootwine, 2013) also showed no clear pattern. 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 was likely the result of the low replication rate 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 (indoors vs. outdoors), differences in ewe BW and BCS prior to experimentation, and the level of undernutrition. All these factors deserve further investigation.

The level of feeding during late pregnancy is critical to achieving optimum lamb birth weights and our meta-analysis showed that failing to meet basic pregnancy nutrition requirements resulted in a decrease of up to 22% in lamb birth weight. Estimates from a meta-analysis of late gestation fetal weight (Gootwine, 2013) showed that late-pregnancy undernutrition can decrease the weight of the fetus close to term by ~27% relative to “untreated” controls. The minor discrepancy in results between meta-analyses is likely due to differences in the study inclusion criteria, studies used for analysis, control groups used for comparison, and the methodology used. Additionally, Gootwine (2013) examined a mix of birth weight and late gestation fetal weight data (i.e., as early as 120 d of gestation), while the meta-analysis reported here examined only birth weight data from naturally born lambs. However, the combined evidence from these meta-analyses suggests that farmers should maintain a PM plane of nutrition during late pregnancy 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 underfed and overfed regardless of the pasture levels being offered. Therefore, determining the optimum feeding level for late pregnancy will depend on the previous nutritional status of the ewe, such as the nutritional level during early pregnancy or midpregnancy and differences in BCS in the flock.

The magnitude of the estimated effects on birth weight for singletons and twins did not differ. Potentially, the inadequate number of data

points for one of the litter sizes was responsible for the absence of observed differences. Indeed, many studies ($n = 34$) were 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 were not presented separately in the manuscript, with only combined main effects being reported. The observation of a similar size effect, however, is sensible because both singleton and twin fetuses achieve a similar proportion of their birth weight at 8, 4, and 2 wk prior to birth (Robinson, 1977), with this effect being 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. Thus, a similar size effect, such as a 500-g decrease in birth weight, can be considered as being more detrimental to the potential performance of a twin lamb compared to a typically heavier singleton. This highlights the importance of identifying singleton and multiple bearing ewes at pregnancy scanning and feeding ewes according to their pregnancy requirements.

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, which manifests as a decreasing treatment effect over time (Ioannidis, 2005). In the present study, this time-lag bias may reflect 2 scenarios: first, research conducted prior to 1990 may have been driven toward nutritional manipulations that were significantly effective at reducing lamb birth weight and, alternatively, it may also reflect the large changes in accepted animal ethics standards that started in the 1950s and were subsequently adopted globally in the late 1980s (Sandoe and Christiansen, 2008), which likely affected the “acceptable” levels of feeding restriction in later years.

The literature considering the effect of maternal overnutrition during pregnancy on lamb birth weight is limited, especially when each stage of pregnancy is considered. Nevertheless, and contrary to our hypothesis, the meta-analysis showed that overnutrition resulted in lambs that were slightly 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. In addition, data for each individual

stage of pregnancy are unavailable, indicating that more experimental evidence is required.

Two additional points deserve consideration. First, in developing nutritional plans that can be applied on-farm, looking solely at the effect on lamb birth weight may neglect other potential effects that undernutrition around this period could have. Although only minor effects were observed on birth weight in the early- and mid-pregnancy subgroups, it is important to note that other effects, likely resulting from the nutritional treatments, were also observed in some of the included studies: reduced lamb viability (Oliver et al., 2005), decreased lambing percentage (Everitt, 1967), and loss of pregnancy (Krausgrill et al., 1999). Second, farmers often rely on periodical measurements of BW and BCS during pregnancy to manage feed allocation. Perhaps, the major limitation of the available literature is the inadequate reporting detail or inconsistency of reporting information related to ewe BW and BCS. Future studies need to ensure these data are reported accurately.

CONCLUSION

The present meta-analysis represents an evidence-based effort to quantitatively combine knowledge from studies of maternal nutrition during pregnancy and its effect on lamb birth weight. Undernutrition in early pregnancy and midpregnancy had only a small and nonsignificant effect on lamb birth weight. In contrast, late-pregnancy undernutrition and long-term undernutrition extending to late pregnancy were associated with a decrease of up to 22% in lamb birth weight. 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. Further studies are required to confirm this.

SUPPLEMENTARY DATA

Supplementary data are available at *Animal Frontiers* online.

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