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Review article

A meta-analytical approach for evaluating the effect of arginine supplementation on the productive performance of sows during gestation

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ABSTRACT

Arginine (Arg) supplementation for gestating and lactating sows seems to play a primary role in litter development by promoting placental vascularization and improving colostrum and milk quality. The aim of this study was to investigate the effects of the supplementation of dietary standardized ileal digestible Arg (SID Arg) on the productive performance of gestating sows using a meta-analytical approach. A total of 19 studies conducted between 2007 and 2020 which tested the effect of additional SID Arg supplementation in diets for sows were chosen using a systematic literature search. Data regarding backfat thickness, number of piglets born and live born, litter birthweight and weaning weight were extrapolated from each experimental group and expressed as a percentage of the value of the control group within the studies. The SID Arg supplementation was expressed as the percentage of SID Arg in the treated group compared to the control group (Additional SID Arg). Linear and quadratic models were built using a mixed procedure utilizing Minitab® software including Additional SID Arg, parity and feed intake classes and the period of SID Arg supplementation as fixed factors, and the study as the random factor. The SID Arg in control groups was higher than the doses suggested by the National Research Council (NRC; 2012) (4.20–8.90 g/kg of feed vs 3.2–7.9 g/kg, respectively). A quadratic response of Additional SID Arg was observed for placental efficiency (PE; P = 0.003; a=0.0019), the number of total piglets born (P = 0.027; a=−0.0003), the number of live born piglets (P = 0.005; a=−0.0006) and backfat thickness loss (P = 0.057; a=0.0029). A linear increase in the plasma concentration of Pro (P = 0.004; b=0.120), Orn (P = 0.002; b=0.284) and Arg (P = 0.001; b=0.425), and a decrease in the concentration of urea (P = 0.037; b=−0.063) was observed with an increasing level of SID Arg. There was no effect on placenta weight, live litter birthweight, individual piglet weight at birth and weaning, litter size and weight at weaning, and average daily gain during lactation. The estimated requirements of SID Arg for improving PE, reducing backfat thickness loss, increasing the number of piglets born and live born were 11.17 g/kg, 13.03 g/kg, 14.83 g/kg and 15.71 g/kg of feed, respectively. This meta-analysis highlighted the importance of redefining the Arg requirements of gestating sows and suggested a dosage ranging from 11.17 to 15.71 g/kg of feed to improve reproductive performance.

Abbreviations: a, coefficient of the quadratic effect; AA, amino acid; ADG, average daily gain; b, coefficient of the linear effect; FI, feed intake; NO, nitric oxide; NRC, National Research Council; PE, placental efficiency; SID, standardized ileal digestible.

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1. Introduction

In recent decades, sow prolificacy has markedly increased due to genetic improvement (Knauer et al., 2012). Increased litter size has led to a higher within-litter variation in birthweight and a higher proportion of low birthweight piglets (Yuan et al., 2015). In fact, increased litter size is negatively correlated with piglet birthweight (Foxcroft et al., 2009). Low birthweight piglets are weaker than normal birthweight piglets and, consequently, an increase in mortality and morbidity occurs (Yuan et al., 2015).

Nutritional strategies during gestation can help minimize these problems. The literature highlights the positive role of functional amino acids (AA) in improved sow productive and reproductive performance (Boutry et al., 2016; Le Floc'h et al., 2018). Functional AA are defined as AA which participate in metabolic pathways and result in improving health, survival, growth and development in growing animals, and gestation and lactation in reproductive animals, including humans and livestock animals (Wu, 2010). According to Wu (2013), functional AA include non-essential AA, essential AA and conditionally essential AA. In pigs, Arg has been classified as a conditionally essential AA by the National Research Council (NRC, 2012). Arg is involved in several metabolic pathways, the urea cycle and, indirectly, in collagen synthesis by the synthesis of Pro (Barbul, 2008). Moreover, Arg is a precursor for several physiological processes, including the production of polyamines and nitric oxide (NO), which exert a stimulating effect on placental angiogenesis (Wu et al., 2017; Elmetwally et al., 2022) as demonstrated by Li et al. (2010). In this study, the placenta of gestating gilts supplemented with Arg (treated 1: 10.2 g/kg and treated 2: 14.2 g/kg vs control group: 6.2 g/kg) showed an increase in terms of the number and diameter of the blood vessels as compared to gilts fed with the control diet. Therefore, Arg may be beneficial in supporting sows during gestation and in improving their performance.

According to the NRC (2012), the Arg requirement for gestating sows depends on parity (second, third and fourth), body weight at insemination, period of gestation (more or less than 90 days) and estimated litter size (from 13.5 to 15.5 piglets). Based on these variables, the Arg requirement, expressed in terms of grams of SID Arg per kilogram of feed, are 6.35 g/kg, 5.5 g/kg and 4.68 g/kg for the second, third and fourth class of parity, respectively. However, considering the evolution of the breed line and the increase in litter size occurring in recent years (Knauer et al., 2012), the Arg nutritional requirement may be greater than estimated by NRC (2012). In a number of studies, Arg supplementation during gestation improved the total number of piglets born (Garbossa et al., 2015; Hong et al., 2020); however, in other studies, Arg supplementation did not improve this parameter (Bass et al., 2017; Hines et al., 2019). In addition, some studies have reported an increase in the number of live born piglets due to Arg supplementation during gestation (Quesnel et al., 2014; Li et al., 2015) whereas other studies have not confirmed this effect (Bass et al., 2017; Moreira et al., 2020). Furthermore, Arg supplementation was associated with a higher litter birthweight (Che et al., 2013; Li et al., 2015). In contrast, other authors have reported no effect (Mateo et al., 2008; Guo et al., 2016) or even a reduction in litter birthweight due to Arg supplementation (Bass et al., 2017). Discrepancies in terms of the effects of Arg supplementation during gestation have been highlighted and have been related to the fact that Arg is involved in several pathways and plays a complex role on the physiology of sows during pregnancy. Therefore, it has been hypothesized that an increase in the dietary level of SID Arg could improve sow performance parameters, including litter size and weight, litter vitality, colostrum, and milk composition, placental efficiency (PE), and weight. Considering the discrepancies in terms of the effects of Arg supplementation during gestation, a meta-analytical approach was chosen as a tool for obtaining quantifiable results regarding the doses of Arg supplementation on different outcomes. The aim of the present meta-analysis was to organize and analyze the data available in the literature and to provide indications regarding the opportunity of revising the SID Arg requirement for gestating sows.

2. Material and methods

2.1. Data collection and dataset building

To choose the studies to include in the meta-analysis, a preliminary systematic literature review was carried out from studies published from 2007 to 2020 following the general guidelines of "systematic literature review" (Vesterinen et al., 2014) which are based on the PRISMA flow charts and guidelines (Liberati et al., 2009). Online databases, including Web of Science, Scopus, PubMed, and Google Scholar, were used for the literature review, combining the following keywords: "arginine", "sow", "gilt", "gestating", "gestation" and "litter". A total of 105 publications were identified. Publications having the following criteria were excluded; a) reviews and book chapters; b) duplicates; c) conference papers; d) meeting abstracts; e) full article not available; f) written in a language

Table 1
The parameters required for inclusion of the study into the dataset for the meta-analysis.

Parameters required
Backfat thickness of sows
Placental weight and efficiency
Total number of piglets born
Total number of live born piglets
Number of stillborn piglets
Litter birth and weaning weight
Piglet birth and weaning weight
Colostrum or milk composition
Free AA or urea concentration in the sow plasma

other than English; a total of 53 peer-reviewed articles were retained. Furthermore, to be included in the meta-analysis articles had a) to report at least one of the parameters listed in Table 1; b) not supplying Arg only during lactation; c) report the diet composition. A total of 19 articles were chosen (Fig. 1; Supplementary Table 1).

For each article, the following information was identified and extrapolated:

1) the experimental groups in each article were defined as control group (fed a basal diet) or as treated group (fed the control diet but supplemented with additional Arg). The information regarding the dose of SID Arg in the diets are reported in Table 2. For all the studies included in the meta-analysis, the chemical composition of the diet was recalculated using EvaPig® (2020), based on the table of composition published by Sauvant et al. (2004). This step was carried out since several articles did not report the analysis of the nutrient composition of the diet; therefore, to obtain it and to deal with the error in estimating the nutrient composition of the diets, it was recalculated on the bases of a single database (Van Milgen et al., 2012; Luise et al., 2021; Oliveira Telesca Camargo et al., 2023). Determining the nutrient composition of the diets allowed determining the percentages of standardized ileal digestible Lys (SID Lys) and SID Arg which were basic data needed to carry out the statistical analysis required by the present meta-analysis. To determine the additional supplementation doses of SID Arg for all the treated groups within each study, the variable Additional SID Arg was calculated using the following equation:

Additional SID Arg = (SID Arg Treated – SID Arg Control) / SID Arg Control * 100

This procedure was adopted because it considerably reduced variation among experiments in the database (Andretta et al., 2016; Luise et al., 2021; Oliveira Telesca Camargo et al., 2023).

2) the parity of the sows in each article was divided into two classes as follows: A= multiparous sows and B= primiparous sows.
3) the duration of Arg supplementation ranged from a minimum of 11,5 days to a maximum of 114 days. The period of Arg supplementation was divided into three categories as follows: 1 = Arg supplementation during the first 60 days of gestation; 2 = Arg supplementation between days 61 and 114 of gestation and 3 = Arg supplementation during the entire gestation period.
4) the daily feed intake (FI) was divided into two classes as follows: low FI (L) if the sows were fed ≤ 2 kg of feed per day; high FI (H) if the sows were fed > 2 kg per day.

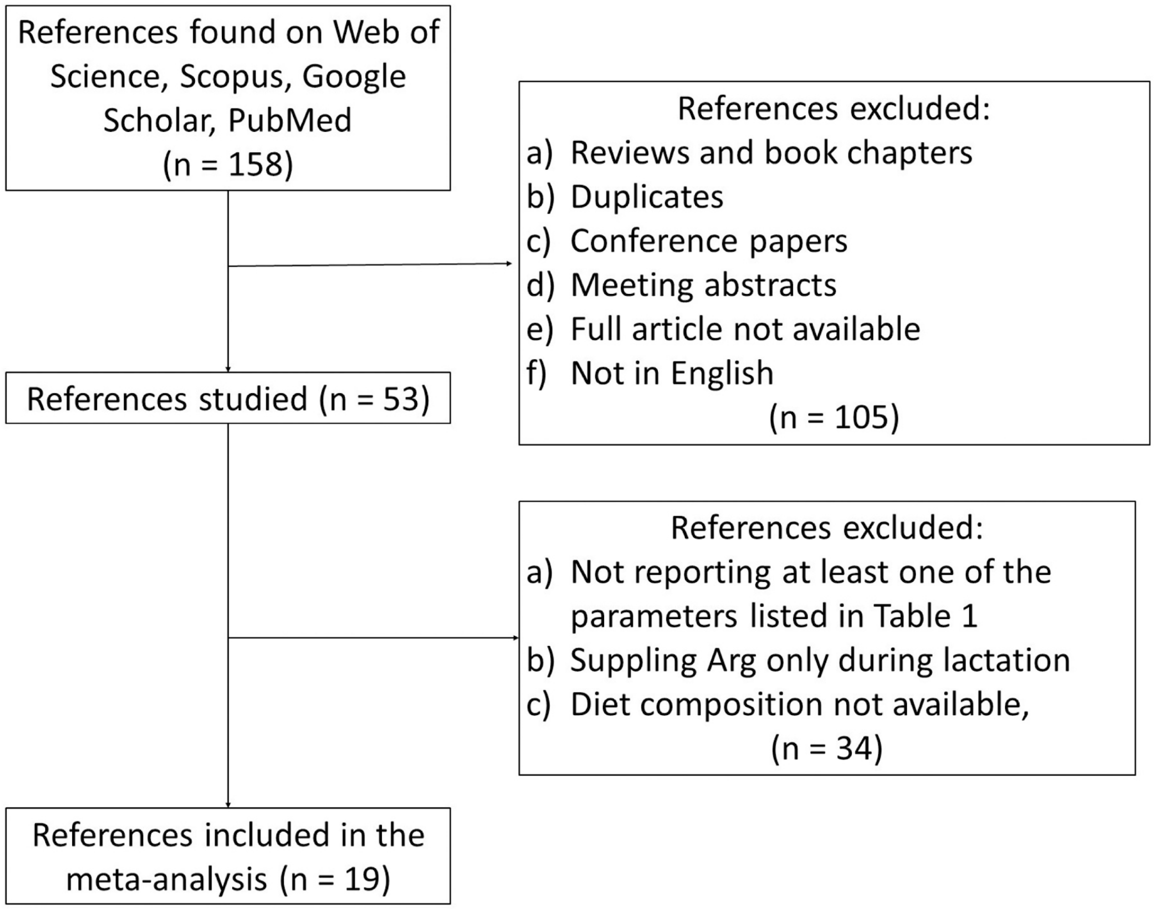

Fig. 1. Flow chart for the selection of the articles included in the meta-analysis.

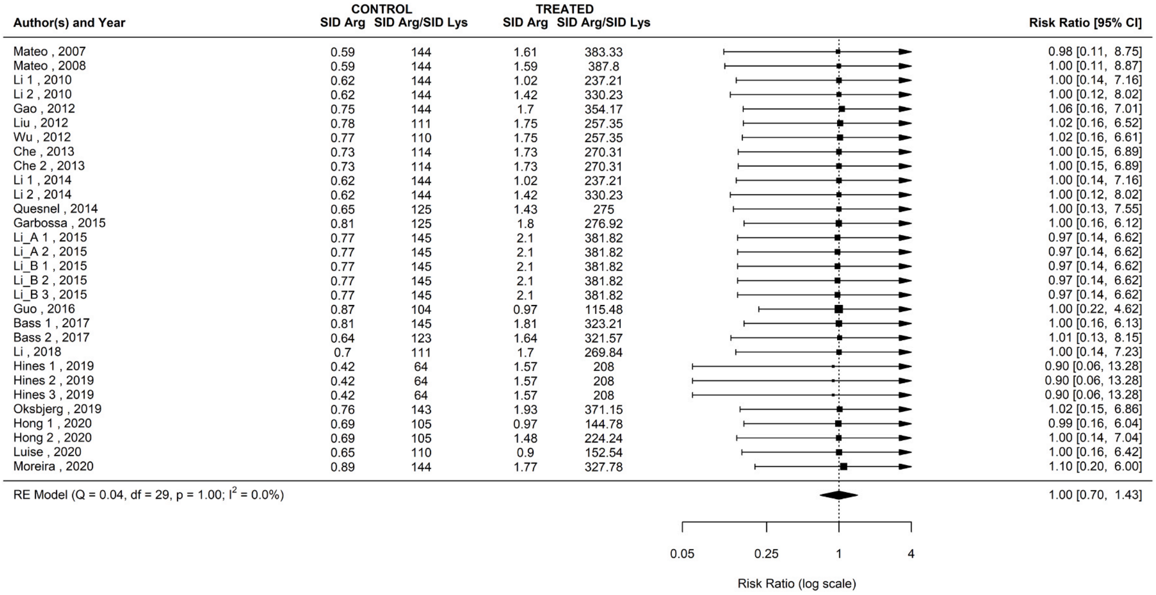

Fig. 2. Forest plot of meta-analysis of Arg supplementation in gestating sows' diet. The square shown for each study (first author and year of publication) is in the risk ratio (RR) for SID Arg (standardize ileal digestible Arginine) and SID Arg / SID Lys ratio in control and treated groups, and the corresponding horizontal line is the 95% CI. Studies with more than one treated group were numbered (author, 1, year of publication) and (author, 2, year of publication). The inclusion of sows or gilts was indicated with A or B, respectively. Che et al. (2013), Li et al. (2015) and Hines et al. (2019) supplemented the same dose of SID Arg in the treated groups but in different periods of gestation.

5) All the data selected regarding sow performance at farrowing and at weaning were expressed as relative values to those observed in the control group, by applying the same equation used for calculating the Additional SID Arg (Andretta et al., 2016; Luise et al., 2021; Oliveira Telesca Camargo et al., 2023). When not available, individual and litter bodyweight, and average daily gain (ADG) were calculated using the data provided in the articles. PE was obtained by dividing the placental weight by the total number of piglets born. The loss of sow backfat thickness was extrapolated or calculated and expressed as the difference between the value for backfat at the beginning of the trial and the value at the end of the trial (mm). The plasma concentration of urea, free Arg and of the AA connected to the Arg metabolism, including Pro and Orn, at the end of the period of Arg supplementation was extrapolated. For all the articles, except one, AA and urea were analyzed within 2 h following the last meal of the sows. Colostrum and milk composition were also determined in some experiments; however, the number of records available was scarce and not enough to be statistically analyzed.

2.2. Statistical analysis

The heterogeneity on both the SID Arg and SID Arg / SID Lys ratio among the diets in the different studies was measured statistically using the metafor (Viechtbauer, 2010) package of RStudio. The risk ratio (RR) for both SID Arg and SID Arg / SID Lys ratio in control and treated groups and their 95% CI were evaluated. Studies with more than one treated group were numbered (author, 1, year of publication) and (author, 2, year of publication). The inclusion of sows or gilts was indicated with A or B, respectively. Results were visualized using a forest plot.

Data were fitted using a linear and quadratic mixed model followed by an ANOVA analysis on Minitab®18 Statistical Software (Minitab®, LLC, 2018).

To apply a quadratic model, the Additional SID Arg^2 factor was created as follows:

$$\text{Additional SID Arg}^2 = \text{Additional SID Arg} * \text{Additional SID Arg}$$

For data regarding sow performance at farrowing, the model included the Additional SID Arg (linear and quadratic models), the class of parity (A or B), the period of Arg supplementation (1, 2 or 3) and the categories of daily FI of the sows (L or H) as fixed factors; the quantity of SID Lys and SID Arg of the control groups were included as covariates, and reference (general encoding referred to the study) was included as the random factor. For the data regarding sow performance at weaning, the piglets' birthweight and the number of live born piglets were included as covariates in addition to the factors described in the previous model; however, they were not significant.

The variations across and within studies for the other AA were not relevant and were therefore not included as factors in the statistical analysis. After a first analysis, non-significant factors, namely the period of Additional SID Arg administration, SID Lys and SID Arg levels in the control diet, and references were removed. The results of the quadratic model were removed when that model

Table 2
Dose of SID Arginine in the diets of the groups included in the meta-analysis and observed parameters.

Reference	Group	SID Arg g/kg feed	Parameters observed
Mateo et al. (2007)	Control	5.9	Backfat thickness, litter and piglets performance at birth, plasma concentration of AAs
	Treated	16.1	
Mateo et al. (2008)	Control	5.9	Litter and piglets performance at birth and at weaning
	Treated	15.9	
Li et al. (2010)	Control	6.2	Placenta weight, urea concentration in plasma
	Treated	10.2	
	Treated	14.2	
Gao et al. (2012)	Control	7.5	Placenta weight, backfat thickness, litter and piglets performance at birth, plasma concentration of AAs
	Treated	17	
Liu et al. (2012)	Control	7.8	Litter and piglets performance at birth, plasma concentration of AAs
	Treated	17.5	
Wu et al. (2012)	Control	7.7	Litter and piglets performance at birth
	Treated	17.5	
Che et al. (2013)	Control	7.3	Litter and piglets performance at birth, plasma concentration of AAs
	Treated	17.3	
	Treated	17.3	
Li et al. (2014)	Control	6.2	Placenta weight
	Treated	10.2	
	Treated	14.2	
Quesnel et al. (2014)	Control	6.5	Backfat thickness, litter and piglets performance at birth and at weaning
	Treated	14.3	
Garbossa et al. (2015)	Control	8.1	Backfat thickness, litter and piglets performance at birth and at weaning
	Treated	18	
Li et al. (2015); (trial 1)	Control	7.7	Backfat thickness, litter and piglets performance at birth
	Control	7.7	
	Treated	21	
	Treated	21	
Li et al. (2015); (trial 2)	Control	7.7	Backfat thickness, litter and piglets performance at birth, plasma concentration of AAs
	Treated	21	
	Treated	21	
	Treated	21	
Guo et al. (2016)	Control	8.7	Placenta weight, litter and piglets performance at birth, plasma concentration of AAs and urea
	Treated	9.7	
Bass et al. (2017); (trial 1)	Control	8.1	Placenta weight, litter and piglets performance at birth and at weaning, plasma concentration of urea
	Treated	18.1	
Bass et al. (2017); (trial 2)	Control	6.4	Litter and piglets performance at birth
	Treated	16.4	
Li et al. (2018)	Control	7	Placenta weight, piglets performance at birth, plasma concentration of AAs
	Treated	17	
Hines et al. (2019)	Control	4.2	Litter and piglets performance at birth and at weaning
	Treated	14.5	
	Treated	14.5	
	Treated	14.5	
Oksbjerg et al. (2019)	Control	7.6	Piglets performance at birth and at weaning
	Treated	19.3	
Hong et al. (2020)	Control	6.9	Placenta weight, backfat thickness, litter and piglets performance at birth and at weaning, plasma concentration of AAs and urea
	Treated	9.7	
	Treated	14.8	
Luise et al. (2020)	Control	6.5	Placenta weight, litter and piglets performance at birth and at weaning
	Treated	9	
Moreira et al. (2020)	Control	8.9	Placenta weight, backfat thickness, litter and piglets performance at birth
	Treated	17.7	

SID Arg, standardized ileal digestible Arginine; Treated, group supplemented with SID Arg. Studies by Che et al. (2013), Li et al. (2015) and Hines et al. (2019) supplemented the same dose of SID Arg in the treated groups but in different periods of gestation.

explained less than the linear model.

The data were analyzed to estimate the Additional SID Arg level needed to maximize sow performance at farrowing and weaning by regression analysis using the quadratic models. To determine the level of Additional SID Arg needed to maximize sow performance, the following equation was utilized: Additional SID Arg optimum dose = (-b)/(2 *a) where b was the coefficient of the linear effect and a was the coefficient of the quadratic effect. Both coefficients were obtained using statistical analysis for each response parameter.

The effects were considered to be significant when $P \leq 0.05$ whereas, when $P > 0.05$ but ≤ 0.10, the differences were considered to indicate a trend towards a significant effect.

3. Results

The amount of SID Arg in the control groups ranged from 4.20 to 8.90 g/kg of feed whereas the quantity of SID Arg in the treated groups ranged from 9.0 to 21.0 g/kg of feed. The minimum and the maximum of the ratio SID Arg / SID Lys in the control groups were equal to 0.64 and 1.46, respectively whereas, for the treated groups, they were equal to 1.16 and 3.88, respectively. As concerns the Additional SID Arg, the minimum, the median and the maximum were equal to 0.115, 1.330 and 2.452- fold respectively (Table 3).

Forest plot in Fig. 1 shows absence of statistical heterogeneity in the RR for the effect of SID Arg supplementation during sows' gestation (Q=0.04; P = 1.00; I^2 =0.0%). The effect of Arg supplementation, parity, and FI on sow performance at farrowing are reported in Table 4. The number of stillborn piglets was removed due to the low number of studies in which it was analyzed, and the low prediction obtained by applying both the linear and quadratic models. The Additional SID Arg did not affect the placenta weight, either the total or the live litter birthweight, or piglet birthweight. Conversely, the Additional SID Arg ^{2} affected PE (P = 0.003; a=0.0019), the number of piglets born (P = 0.027; a=−0.0003) and the number of live born (P = 0.005; a=−0.0006) tended to reduce the backfat thickness loss during gestation (P = 0.057; a=0.0029). The quadratic model estimated that the Additional SID Arg which maximized the response to Arg supplementation for PE, backfat, number of piglets born and number of live born were 0.6 fold (R^2 Adj,%=55.8), 0.86 fold (R^2 Adj,%=37.6), 1.125 fold (R^2 Adj,%=21.5) and 1.25 fold (R^2 Adj,%=34), respectively, compared to the SID Arg value in the control group. Considering that the average value of SID Arg in the control groups included in the meta-analysis was 6.98 g/Kg, these percentages corresponded to additional doses of 4.19 g/kg, 6.00 g/kg, 7.85 g/kg and 8.73 g/kg of SID Arg to the control dose in the feed to maximize PE, backfat, number of piglets born and live born, respectively.

The class of parity did not affect the parameters investigated but tended to increase the litter birthweight (P = 0.056; A=7.00; B=3.64) and live litter birthweight (P = 0.077; A=7.75; B=5.54). The class of FI tended to affect the live litter birthweight (P = 0.054; H=5.01; L=8.28) and the piglet birthweight (P = 0.051; H=−0.37; L=2.44). Moreover, the number of piglets born increased the litter birthweight (P < 0.001) and the number of live born piglets increased the live litter birthweight (P < 0.001). Table 5 shows the effects of the Additional SID Arg and of the period of its supplementation on the blood parameters of the sows at the end of the period of Arg supplementation. The Additional SID Arg increased linearly the concentration of Pro (P = 0.004; b=0.120), Orn (P = 0.002; b=0.284) and Arg (P = 0.001; b=0.425) and decreased linearly the concentration of urea (P = 0.037; b=−0.063) in the blood of the sows. The gestation period was significant only for the concentration of urea (P = 0.005; 1 =−11.77; 2 =9.15).

Litter size at weaning, pig weaning weight, litter weaning weight and ADG were not affected by the Additional SID Arg (Table 6). No effects of parity were observed on any of the parameters analyzed.

4. Discussion

A meta-analysis is a powerful tool for obtaining information from the literature regarding a specific topic by having a statistical support to justify the effects observed (Haidich, 2010; Gopalakrishnan and Ganeshkumar, 2013). In the present meta-analysis, the effects of SID Arg supplementation on sow productive performances were investigated. This meta-analysis highlighted that the SID Arg requirement to maximize sow productive performance is higher than the value reported by the NRC (2012). In fact, all the studies included in the present dataset used a SID Arg / SID Lys ratio of between 0.64 and 1.46 in the control groups, which is greater than the average value suggested by the NRC (2012) which is 0.53.

The supplementation of SID Arg to the sow diet can increase the number of piglets born and the number of live born piglets at farrowing regardless of the time of supplementation in dose dependent way. This result was in contrast with Wu et al. (2013) who reported that the period of Arg supplementation was statistically significant and affected productive performance of sows at farrowing; the lack of a significant effect of the period of Arg supplementation in the present study could have been due to the limited number of studies.

The increased number of live born piglets could improve sow productivity, resulting in improved economic return for swine production (Amer et al., 2014). Therefore, improving embryonic implantation and development during the peri-implantation period of pregnancy and proper intrauterine development of the fetus is of great interest (Bazer et al., 2010; Wang et al., 2012). These traits can be influenced by non-genetic factors, including the management and feeding of gilts and sows (Lawlor and Lynch, 2007). Hou et al. (2016) reported that supplementing gestating sows with functional AA including Arg, Gln, Glu, Gly and Pro, improved fetal survival and growth. The positive effect of dietary SID Arg observed in the present meta-analysis on the number of live born piglets could have

Table 3
Results of descriptive analysis based on data extrapolated from the 19 studies selected.

Variable	Mean	SEM	StDev	Minimum	Median	Maximum
Arg supplementation (days)	47.24	4.31	30.78	11.00	30.00	114.00
SID Arg Control group, g/kg	6.988	0.159	1.149	4.20	7.30	8.90
SID Lys Control group, g/kg	5.704	0.222	1.063	4.10	5.30	8.40
SID Arg/ SID Lys, Control group	1.277	0.044	0.212	0.64	1.43	1.46
SID Arg Treated group, g/kg	15.997	0.653	3.574	9.00	16.70	21.00
SID Lys Treated group, g/kg	5.737	0.195	1.070	4.10	5.50	8.40
SID Arg/ SID Lys, Treated	2.882	0.145	0.794	1.15	2.76	3.88
Additional SID Arg, fold	1.368	0.103	0.566	0.11	1.33	2.45

SID Arg, standardized ileal digestible Arginine.

Table 4
Effects of Arginine supplementation on sows' productive performance at farrowing.

Item	*n*	R^2 Adj, %	P-value						Coefficients	
									b	a
			Additional SID Arg	Additional SID Arg^2	Parity	Feed Intake	Number of piglets born	Live born piglets	Additional SID Arg	Additional SID Arg^2
Placental weight	9	48.24	0.388	0.467	0.914	0.908	–	–	0.165	-0.001
PE	7	60.16	0.004	0.003	0.366	–	–	–	-0.237	0.0019
Backfat loss	8	41.49	0.038	0.057	0.586	0.252	–	–	-0.519	0.0029
Total number of piglets born	17	39.85	0.005	0.027	0.372	0.120	–	–	0.094	-0.0003
Total number of live born piglets	16	38.20	0.001	0.005	0.904	0.244	–	–	0.145	-0.0006
Litter birthweight	17	82.86	0.024	–	0.056	0.639	< 0.001	–	0.019	–
Live litter birthweight	16	82.08	0.319	–	0.077	0.054	–	< 0.001	0.008	–
Piglet birthweight	18	20.85	0.682	0.487	0.278	0.051	–	–	-0.009	0.000

PE: placental efficiency was obtained by dividing the placental weight by the total number of piglets born
n: number of studies that include the parameter
R^2 Adj, %: R^2 of the Mixed Linear Model
SID Arg, standardized ileal digestible ArginineAdditional SID Arg was obtained by the equation: (SID Arg Treated – SID Arg Control) / SID Arg Control x 100
Additional SID Arg^2 was obtained by the equation: Additional SID Arg x Additional SID Arg
Parity: primiparous (gilts) or multiparous (sows)
Feed Intake: the quantity of feed supplemented in sows during gestation: L= $\leq$2 kg of feed per day; H= $>$2 kg of feed per day
The total number of piglets born was used as a covariate regarding litter birthweight.
The total number of live born piglets was used as a covariate regarding live litter birthweight
b: coefficient of the linear effect
a: coefficient of the quadratic effect

Table 5
The effects of Arginine supplementation on the concentration of free amino acids and urea in the plasma of sows during the final period of Arg supplementation.

Item	*n*	R^2 Adj, %	P-value		Coefficient
					b
			Additional SID Arg	Gestation period	Additional SID Arg
Proline	8	35.34	0.004	0.657	0.120
Ornithine	7	38.61	0.002	0.438	0.284
Arginine	7	53.66	0.001	0.505	0.425
Urea	8	51.02	0.037	0.005	-0.063

n: number of studies which included the parameter
R^2 Adj, %: R^2 of the Mixed Linear Model
SID Arg, standardized ileal digestible ArginineAdditional SID Arg was obtained by equation (SID Arg Treated – SID Arg Control) / SID Arg Control x 100; the quadratic effect was never statistically significant and was excluded.
Gestation period: period of Arg supplementation during gestation: 1 = Arg was supplemented during the first 60 days of gestation; 2 = Arg was supplemented between days 61 and 114 of gestation; 3 = Arg was supplemented during the entire gestation period.
b: coefficient of the linear effect.

been due to its involvement in the antioxidative pathways for the promotion of placental growth (including vascularization) and uteroplacental blood flow (Wu et al., 2013). Moreover, during pregnancy, utero-placental blood flow increases and, to support it, placental angiogenesis increases from the first to the second and the third trimesters of gestation until the last days of gestation (Wu et al., 2013). An impaired placental blood flow can affect the growth and survival of the fetus, therefore compromising litter size at birth (Wu, 2009; Wu et al., 2013). This meta-analysis confirmed the positive effects of SID Arg supplementation on PE which could be related to the increase in the placental blood flow as reported by Elmetwally et al. (2022). As exhaustively reviewed by Wu (2013) and Wu et al. (2013), Arg is a physiologically versatile AA which can be catabolized to synthetize several bioactive molecules, including polyamines, NO, creatine and Orn, which are involved in placental angiogenesis. Overall, NO acts as a vasodilator (Wu et al., 2017), promoting placental angiogenesis, dilation and the dimensions of the blood placental vessels, increasing the blood flow as shown by Li et al. (2014), and stimulates cell proliferation. NO is also involved in the embryonic implantation process and in the ratio of locally produced progesterone and estradiol (Luo et al., 2021). Polyamines derived from Arg (putrescine, spermine and spermidine), can positively influence placental angiogenesis and placental vascularization, resulting in a better utero-placental blood flow (Reynolds et al., 2006; Elmetwally et al., 2022). The same trend has been observed in mice by Zeng et al. (2008) who reported that Arg supplementation during the entire gestation period, or between days 1 and 7 of gestation, increased embryonic survival and birth litter size by 30% as compared to mice in the control group.

The estimated peak response for the number of live born piglets was at 1.25 fold of the SID Arg as compared to the doses of SID Arg used in the control groups. Considering that the average SID Arg in the control groups was 6.98 g/kg, the estimated SID Arg to maximize the number of live born piglets would be 15.71 g/kg (6.98 g/kg + 8.725 g/kg which is the 1.25 fold). Therefore, considering that the average feed intake at this stage of production is 2.5 kg/day, the daily dose per sow would correspond to 39.28 g/sow/day. An additional increase in SID Arg would lead to a lesser or even a negative effect on the number of live born piglets. This result could be

Table 6
The effects of Arginine supplementation on piglet productive performance at weaning.

Item	*n*	R-sq Adj, %	P-value					Coefficients	
								b	a
			Additional SID Arg	Additional SID Arg^2	Piglet birth weight	Parity	Live born Piglets	Additional SID Arg	Additional SID Arg^2
Litter size at weaning	6	11.66	0.369	0.376	–	0.609	0.912	0.034	-0.000
Pig weaning weight	7	5.46	0.202	0.283	0.333	0.736	–	0.073	-0.000
Litter weaning weight	5	18.59	0.748	0.563	0.599	0.669	–	-0.053	0.001
Piglet ADG	5	17.34	0.903	0.918	–	0.727	0.775	0.060	-0.000

n: number of studies which included the parameter
R-sq Adj, %: Squared of the Mixed Linear Model
SID Arg, standardized ileal digestible ArginineAdditional SID Arg was obtained using the equation (SID Arg Treated – SID Arg Control) / SID Arg Control x 100
Additional SID Arg ^{2} was obtained using the equation: Additional SID Arg x Additional SID Arg
Piglet birthweight was used as a covariate for pig weaning weight and litter weaning weight
Parity class: primiparous (gilts) or multiparous (sows)
b: coefficient of the linear effect
a: coefficient of the quadratic effect

due to the interference of such high Arg levels on the intestinal absorption or metabolism of other essential AA, including a competition for the intracellular transport between Arg and Lys (Luiking and Deutz, 2007) as reported for growing pigs (Hagemeier et al., 1983). However, a high dietary Arg dose, up to 2.14 g/kg body weight, is well tolerated by pregnant sows (Wu et al., 2007). Moreover, it has been reported in other species that Arg induced an overstimulation of the NO synthesis pathway, causing an excessive production of reactive oxygen species, NO-mediated vasodilation, hypotension and hemodynamic instability (Luiking and Deutz, 2007). However, NO synthesis is difficult to measure because it is a very labile compound which is rapidly oxidized to nitrite and nitrate in blood (Luiking and Deutz, 2007).

The estimated peak response for the number of total piglets born was 1.125 fold of the SID Arg in the control groups resulting in a dose of 7.89 g/kg of SID Arg, therefore the estimated SID Arg to maximize the number of total piglets born would be 14.83 g/kg. This estimated dose is lower than that found to maximize the number of live born piglets. This may be explained by the inclusion of stillborns in the total number of piglets born; in fact, as stated before, Arg is not only required for protein synthesis but also for Pro, Orn, Gln and Glu syntheses which are essential for fetal growth (Deutz, 2008; Wu et al., 2007).

Placental efficiency represents an important physiological target for sustaining fetal development. The calculated Additional SID Arg needed to maximize the response to Arg supplementation for PE was 0.60 fold to the SID Arg used in control groups of the studies included in the meta-analysis. Considering that the average SID Arg in the control groups was 6.98 g/kg, the estimated peak response would be 11.17 g/kg SID Arg feed (6.98 g/kg plus 4.19 g/kg which is the 0.60 fold) which is less than the dose needed to increase the number of live born piglets. This could mean that, to optimize placental vascularization, less Arg than that required to maximize the oocyte implantation, or to sustain fetal growth and development is required. However, the results obtained for PE should be considered carefully since the number of studies reporting this characteristic was lower than the number of studies reporting the number of live born piglets per litter.

Arg supplementation above the suggested requirements could improve litter birthweight without any estimated peak response. In fact, the quadratic model was not significant, and it was not possible to determine the dose needed to maximize the response. The increase in litter weight at birth is related to the increase in the total number of piglets born and/or the number of piglets born live. Interestingly, an increase in SID Arg did not increase piglet birthweight but neither did it reduce piglet birthweight, which could also be expected. In fact, an increase in litter size is related to a decreased birthweight (Milligan et al., 2002). Furthermore, Arg supplementation could increase piglet litter size without compromising birthweight. This is important because a low birthweight results in an increase in terms of piglet morbidity and mortality rates, and reduced growth performance (Boulot et al., 2008; Škorput et al., 2018).

Increasing dietary SID Arg reduced backfat thickness loss. Supplying gestating sows with Arg doses higher than those suggested by the NRC (2012) could reduce the mobilization of subcutaneous fat which results in a lesser difference between the initial backfat thickness and the final backfat thickness of gestating sows. In this regard, it has been shown that Arg is involved in the regulation of the fat metabolism (Hu et al., 2019), and its supplementation decreases body fat accumulation in pigs (Tan et al., 2009). Furthermore, dietary Arg supplementation increases the expression level of the gene related to lipolysis (hormone-sensitive lipase) and simultaneously decreases the expression level of the gene related to lipogenesis in subcutaneous adipose tissue (acetyl-CoA carboxylase; Tan et al., 2011). However, these studies refer to growing pigs and not to gestating sows which have to recover from the loss of the backfat occurring during lactation.

According to Wu (2013) and Wu et al. (2013), Arg is a physiologically versatile AA which can be converted into several different AA. In the present meta-analysis, it was possible to evaluate the effect of Arg supplementation on the plasma concentration of AA related to the Arg metabolism, including Orn and Pro. Wu (2009) asserted that Arg was transported into the enterocytes and converted into Orn, Pro and urea. These compounds were then transported to the portal vein and thereafter into the blood stream. This explained why the increase in nutritional Arg increased the plasma levels of Pro, Orn and Arg in plasma, confirming that Arg could be used as precursor for Pro and Orn in gestating sows. Moreover, the typical Arg catabolism pathway is initiated by arginase to produce Orn which is then used as precursor for the synthesis of Pro and other compounds, such as polyamines, Gln and Glu (Morris, 2006; Wu, 2013).

Regarding urea, the increase in SID Arg reduced its concentration in the blood. Urea can be produced during the catabolism of Arg to Orn (Wu, 2009). The negative relationship between dietary Arg and the urea levels in sow plasma could be due to an improvement in the efficiency of nutrient utilization for enhancing tissue protein synthesis due to Arg supplementation (Kim et al., 2004). Since urea is one of the main nitrogenous products of AA catabolism, this explains why its plasma concentration is lower when dietary Arg is increased. The same negative correlation between Arg supplementation and urea levels in plasma has been observed in premature infants (Zamora et al., 1997) and in piglets (Kim et al., 2004).

The additional SID Arg did not affect sow performance parameters during lactation and at weaning. This result may have been due to the limited number of studies included in the meta-analysis and highlighted the need of additional studies to evaluate the effects of Arg supplementation during both gestation and lactation on sow and litter performance at weaning. Moreover, the performance parameters at weaning depend on several factors and, for this reason, can be considered challenging phenotypes. Sow daily FI, colostrum and milk quality and quantity, the availability of creep feed, piglet weaning age and ambient temperature are just some of the aspects which impact performance at weaning (Turpin et al., 2016; Hojgaard et al., 2020; Rauw et al., 2020; Amatucci et al., 2022).

5. Conclusions

Overall, although this meta-analysis has some limitations due to the limited number of studies for some response parameters and the statistical approach that did not estimate heterogeneity for all response parameters, the results underline the importance and relevant role that Arg may have in pregnant sows. The Arg supplementation in diets for gestating sows improved the productive performance of both sows and piglets, especially in terms of litter size at birth and backfat loss, confirming the key role of this amino acid in supporting the physiological modification of the sows during pregnancy as well as the impact on fetal development. In addition, this meta-analysis highlighted the issues which deserve additional investigation including the effect of Arg supplementation on colostrum and milk quality and sow performance at weaning. Finally, there was no complete correspondence between the SID Arg requirements reported by the NRC (2012); 3.2–7.9 g/kg) and the amount of SID Arg used in the control groups of the studies included in the meta-analysis (4.20–8.90 g/kg). According to the present meta-analysis, the total estimated requirements of SID Arg for improving placental efficiency, reducing backfat thickness loss, increasing the total number of piglets born, and number of live born are 11.17 g/kg, 13.03 g/kg, 14.83 g/kg and 15.71 g/kg of feed, respectively. Care should be taken for the results obtained regarding placental efficiency and backfat thickness because of the low number of studies included in the model.

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CRediT authorship contribution statement

Sara Virdis: Investigation, Writing – original draft, Formal analysis; **Diana Luise**: Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing; **Paolo Bosi**: Conceptualization, Methodology, Writing – review & editing; **Paolo Trevisi**: Investigation, Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.anifeedsci.2023.115807.

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