

A meta-analysis of genetic parameter estimates for milk and serum minerals in dairy cows

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Research Article

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Abstract

This study aimed to conduct a meta-analysis based on a random-effects model to combine different published heritability estimates and genetic correlations for milk and serum minerals in dairy cows. In total, 59 heritability and 25 genetic correlation estimates from 12 articles published between 2009 and 2021 were used. The heritability estimates for milk macro-minerals were moderate to high and ranged from 0.311 (for Na) to 0.420 (for Ca). On the other hand, milk micro-minerals had lower heritabilities with a range from 0.013 (for Fe) to 0.373 (for Zn). The heritability estimates for serum macro-minerals were generally low and varied from 0.126 (for K) to 0.206 (for Mg). The estimates of genetic correlation between milk macro-minerals varied from -0.024 (between Na and K) to 0.625 (between Mg and P). The genetic correlations of milk Ca and P with milk yield were -0.171 and -0.211 , respectively. The estimates of genetic parameters reported in this meta-analysis study are appropriate to utilize in breeding plans when valid estimates are not available for milk minerals in dairy cow populations.

Bovine milk is an important source of minerals that are important for human nutrition and dairy product quality (Gaucheron, 2005; Haug *et al.*, 2007; Buitenhuis *et al.*, 2015). Although vitamins are organic substances, minerals are inorganic but are needed solely in minute values. Minerals can be grouped into trace or micro-elements (e.g. Fe, Zn, Se, Mn and I) that are needed in low values, and quantity or macro-elements (e.g. Mg, P, K and Ca) that are needed in greater quantities. When the dietary intakes of macro- and micro-minerals are inadequate, deficiencies can appear that can affect the health of human or animal consumer. Milk mineral concentration is known to differ by numerous variables, such as breed (Carroll *et al.*, 2006; Niero *et al.*, 2016), lactation stage (Carroll *et al.*, 2006; van Hulzen *et al.*, 2009), lactation number (Kume *et al.*, 1998), and udder health situation (Summer *et al.*, 2009).

Milk minerals contribute to numerous essential physiological mechanisms. For example, Ca and P play a significant role in the metabolism of bone, Se and Zn in immune responses and Ca, K, and Mg in blood pressure control (Cashman, 2006; Haug *et al.*, 2007). Moreover, increased levels of milk Na can be a benchmark for mastitis incidence (Gaucheron, 2013). Milk minerals are also related to technological features of milk processing (Jensen *et al.*, 2012). Calcium phosphate impacts physicochemical stability of casein in milk, cheese-making characteristics and milk quality throughout storage (Gaucheron, 2005; Haug *et al.*, 2007). This connection between milk minerals and cheese-making properties is held up by the genetic associations that were reported between them (Sanchez *et al.*, 2018). Modifying Ca levels affected milk stability to heat treatment (Deeth and Lewis, 2015).

The desire to include new phenotypes in the selection objectives for dairy cattle is increasing. Attention to both milk yield and composition as well as animal health and reproductive performance are all important (Fleming *et al.*, 2018) and environmental impact (or lack of it) will come into focus in the future. The inclusion of a new phenotype into a selection program requires the regular phenotyping of the trait at the population level. However, quantifying milk minerals on a large scale needs many resources due to the time and cost of reference laboratory analyses. This possible threat represents a restriction for the estimation of accurate genetic parameters for milk minerals, as well as being able to obtain high accuracy estimates of genetic merit for individual animals (Visentin *et al.*, 2019). Therefore, infrared prediction of milk minerals could be a very important and cheap addition to the collection of milk traits that are presently accessible for farm management and breeding programs (Zaalberg *et al.*, 2021).

Accurate estimates of genetic parameters for economically important traits are mandatory to predict, precisely, the breeding values of animals in the breeding schemes (de Oliveira *et al.*, 2017). Satisfactory knowledge of the genetics underlying the mineral contents of milk and serum in dairy cattle is required to enable enhancements through feeding or breeding systems. Over the previous years, genetic parameter estimates have been reported for milk and serum minerals in dairy cows. However, these estimates have been reported in studies differing in terms of bovine population, breeds, samples size and considering different effects in the model. This has resulted in considerable variability among heritability and genetic correlation

estimates. A meta-analysis considering variability among studies would be considered as an applied and well-planned solution to summarize all studies and overcome the variability problem (Sutton *et al.*, 2000). Using the random-effects model of meta-analysis, it is possible to provide more reliable outputs than those obtained from individual studies (Borenstein *et al.*, 2009; de Oliveira *et al.*, 2017). The reason for designing this study was the need for collecting estimates from previous studies to provide summary genetic parameter estimates for milk and serum minerals to develop breeding objectives in dairy cattle. Also, to prevent unfavorable correlated responses with other economically important traits, understanding the genetic correlations between them and with milk production is necessary before including milk minerals into dairy breeding objectives. To the knowledge of the author, a specific meta-analysis of the genetic parameters for milk and serum minerals has not been reported in the literature. Thus, the objective of this study was to conduct a meta-analysis based on a random-effects model to combine different published heritability estimates for milk and serum minerals and their genetic correlations in dairy cows.

Materials and methods

Description of the study scope and evaluated traits

A systematic search of the literature using electronic databases of ISI Web of Knowledge (<https://apps.webofknowledge.com>) and Google Scholar (<https://scholar.google.com>) was conducted to identify all references reporting estimates of heritability for milk and serum minerals and their genetic correlation in dairy cows. The most exhaustive research query was built, using synonyms and derivatives of the following keywords: 'dairy cow', 'milk minerals', 'milk micronutrients', 'serum minerals', 'genetic parameters', 'heritability', and 'genetic correlation'. In total, 59 heritability and 25 genetic correlation estimates from 12 scientific articles were used in the present study. The considered articles were published between 2009 and 2021 (online Supplementary Table S1). The estimates were derived from restricted maximum likelihood (REML) and Bayesian inference estimation methods on a mixed animal model. Therefore, estimates obtained from reduced models, such as the sire model, were removed. The literature cited in the above-mentioned articles was also checked. Traits included in the study were milk concentrations of calcium (Ca_m), phosphorus (P_m), potassium (K_m), magnesium (Mg_m), sodium (Na_m), copper (Cu_m), manganese (Mn_m), selenium (Se_m), zinc (Zn_m) and iron (Fe_m), and also serum concentrations of calcium (Ca_s), phosphorus (P_s), potassium (K_s) and magnesium (Mg_s).

Data recorded

The data sets included information on direct heritability estimates for milk and serum minerals, genetic correlations between milk minerals and genetic correlations between milk calcium and phosphorus with milk yield, as well as published standard errors for these parameter estimates. Other information recorded was the publication year, journal name, the number of records, breed name, lactation number, country of origin, years of data collection, phenotypic mean and standard deviation, the used estimation method (REML or Bayesian) and model of analysis (univariate or multivariate). When the same estimate was reported in different publications, based on the same database, only the most recent publication was included in the analysis.

Besides that, the meta-analysis was executed only for traits in which the estimates were based on at least two different databases, to minimize the possible impact of non-independence among articles.

For articles in which the standard error for the heritability or correlation estimates were not reported, approximated standard errors were derived by using the combined-variance method (Sutton *et al.*, 2000), which is given by the following formula:

$$SE_{ij} = \sqrt{\frac{\left(\frac{\sum_{k=1}^K s_{ik}^2 n_{ik}^2}{\sum_{k=1}^K n_{ik}} \right)}{n'_{ij}}}$$

where SE_{ij} is the predicted standard error for the published parameter estimate for the i th trait in the j th article that has not reported the standard error, s_{ik} is the published standard error for the parameter estimate for the i th trait in the k th article that has reported the standard error, n_{ik} is the number of used records to predict the published parameter estimate for the i th trait in the k th article that has reported the standard error, and n'_{ij} is the number of used records to predict the published parameter estimate for the i th trait in the j th article that has not reported the standard error.

Phenotypic trait

Means and standard deviations were calculated for all traits using the sample sizes as weights. The total number of records for each phenotypic trait was calculated as the sum of the number of records in each article that reported the trait. The coefficient of variation in percentage ($CV_i(\%)$) for each i th trait was calculated as follows:

$$CV_i(\%) = \frac{s_i}{\bar{X}_i} \times 100$$

where s_i is the standard deviation for the i th trait and \bar{X}_i is the trait mean.

Heritabilities and genetic correlation

Meta-analysis was performed based on a random-effects model (Borenstein *et al.*, 2009) using the Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, USA) to calculate the effect size for genetic parameter estimates. In the random-effects model, observed differences among study results are due to the play of chance in repeated sampling and random changes in real values of parameters (Borenstein *et al.*, 2011). The random-effects model fitted was as follows:

$$\hat{\theta}_j = \bar{\theta} + u_j + e_j$$

where $\hat{\theta}_j$ is the published parameter estimate in the j th article, $\bar{\theta}$ is the weighted population parameter mean, u_j is the among study component of the deviation from the mean, assumed as $u_j \sim N(0, \tau^2)$, where τ^2 is the variance representing the amount of heterogeneity among studies, e_j is the within-study component due to sampling error in the parameter estimate in the j th article, assumed as $e_j \sim N(0, \sigma_e^2)$, where σ_e^2 is the within-study variance.

Table 1. Number of literature estimates (N), measurement units (Unit), the total number of records (Records), weighted mean, standard deviation (SD), and the coefficient of variation (CV) for the concentrations of the minerals in milk and serum of dairy cows

Trait	Unit	N	Records	Mean	SD	CV (%)
Ca _m	mg/kg	12	1 479 133	1196.33	87.72	7.33
K _m	mg/kg	8	1 464 121	1500.27	63.39	4.23
Na _m	mg/kg	7	1 327 005	379.24	76.59	20.20
P _m	mg/kg	12	1 476 752	1047.96	103.83	9.91
Mg _m	mg/kg	9	1 446 598	105.84	11.03	10.42
Se _m	µg/kg	4	3468	18.92	5.52	29.16
Zn _m	µg/kg	4	3471	3939.92	402.74	10.22
Cu _m	µg/kg	2	1287	94.60	41.13	43.48
Fe _m	µg/kg	3	1540	673.62	446.76	66.32
Mn _m	µg/kg	2	1260	32.76	8.24	25.17
Ca _s	mg/kg	2	4610	91.00	6.12	6.72
K _s	mg/kg	2	4414	72.54	59.52	82.06
P _s	mg/kg	2	4645	66.01	31.88	48.30
Mg _s	mg/kg	2	4637	22.41	0.26	1.16
Milk yield	kg/day	2	992 009	22.84	0.35	1.55

'm' and 's' subscripts indicated the concentrations of the minerals in milk and serum, respectively.

Forest plots were constructed to indicate the effect size for each study. Effect sizes for forest plots were the mean heritability estimates for milk and serum minerals or genetic correlation estimates at a 95% confidence interval using the random-effects model.

Heterogeneity

Chi-square (Q) test and the I^2 statistic were determined to measure heterogeneity (Borenstein *et al.*, 2011). Variations among the study level were assessed using a Q test. The significance level was set at 0.10 because the Q test has relatively low power when a small number of studies are included (Huedo-Medina *et al.*, 2006; Lean *et al.*, 2009). Although the Q test helps identify heterogeneity, the measure I^2 was used to measure heterogeneity as follows (Lean *et al.*, 2009):

$$I^2(\%) = \frac{Q - (k - 1)}{Q} \times 100$$

where Q is the χ^2 heterogeneity statistic and k is the number of studies. Q is the Q statistics given by the following formula:

$$Q = \sum_{j=1}^k w_j (\hat{\theta}_j - \bar{\theta})^2$$

where w_j is the parameter estimate weight (assumed as the inverse of published sampling variance for the parameter, $\frac{1}{s_j^2}$) in the j th article; $\hat{\theta}_j$ and $\bar{\theta}$ were defined above in the random-effects model, and k is the number of used articles. The I^2 statistic describes the percentage of variation across studies due to heterogeneity. Negative values of I^2 are set equal to zero; consequently, I^2 lies between 0 and 100% (Lean *et al.*, 2009). Its value might not be important if it falls within the range of 0–40%. However, a value of 30–60% often indicates moderate heterogeneity,

50–90% might represent substantial heterogeneity, and a value in the range of 75–100% represents considerable heterogeneity (Higgins and Green, 2011).

Results

Descriptive statistics

The number of literature estimates, measurement units, the total number of records, weighted mean, standard deviation, and the coefficient of variation for the concentrations of the minerals and milk yield of dairy cows are shown in Table 1. The weighted coefficients of variation for milk macro-minerals were generally low and varied from 4.23 (for K_m) to 20.20% (for Na_m). In general, micro-minerals of milk had greater weighted coefficients of variation which ranged from 10.22 (for Zn_m) to 66.32% (for Fe_m). For serum minerals, Mg_s and Ca_s had low weighted coefficients of variation (1.16 and 6.72%, respectively), but P_s and K_s had high values (48.30 and 82.06%, respectively). In addition, the weighted coefficient of variation for milk yield was low (1.55%) in this study.

Heritability estimates

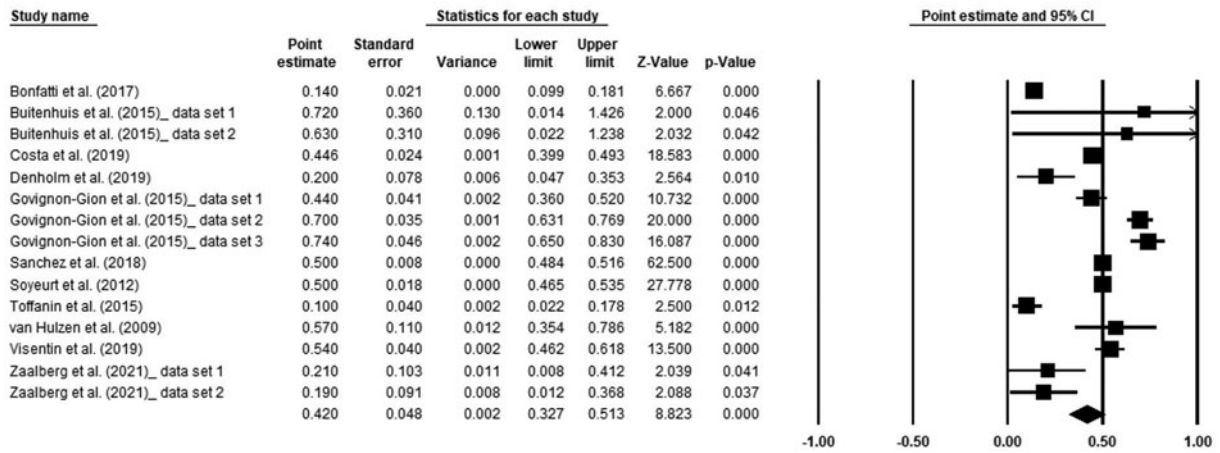
Effect size and heterogeneity of the heritability estimates (based on Q and I^2 statistics) for the concentrations of minerals in milk and serum of dairy cows obtained from the random-effects model of the meta-analysis are presented in Table 2. The heritability estimates for milk macro-minerals were moderate to high and ranged from 0.311 (for Na_m) to 0.420 (for Ca_m). On the other hand, milk micro-minerals had lower heritabilities with a range from 0.013 (for Fe_m) to 0.373 (for Zn_m). The heritability estimates for serum macro-minerals were generally low and varied from 0.126 (for K_s) to 0.206 (for Mg_s). The evaluation of heritability estimates for minerals showed that macro-minerals

Table 2. Effect size and heterogeneity of the heritability estimates for minerals in milk and serum of dairy cows obtained from the random-effects model of meta-analysis

Trait	N	h^2	SE	95% CI	P-value	Q	P-value	I^2
Ca _m	15	0.420	0.048	0.327–0.513	0.000	459.305	0.000	96.952
K _m	8	0.327	0.075	0.181–0.474	0.000	523.969	0.000	98.664
Na _m	7	0.311	0.020	0.272–0.350	0.000	15.920	0.014	62.310
P _m	12	0.387	0.049	0.290–0.483	0.000	303.160	0.000	96.372
Mg _m	9	0.383	0.062	0.262–0.504	0.000	348.148	0.000	97.702
Se _m	4	0.171	0.048	0.076–0.266	0.000	0.399	0.940	0.000
Zn _m	4	0.373	0.069	0.238–0.507	0.000	2.491	0.477	0.000
Cu _m	2	0.043	0.028	0.000–0.098	0.123	0.910	0.340	0.000
Fe _m	3	0.013	0.027	0.000–0.067	0.642	0.535	0.765	0.000
Mn _m	2	0.140	0.038	0.065–0.214	0.000	0.003	0.954	0.000
Ca _s	2	0.173	0.038	0.098–0.247	0.000	2.285	0.131	56.234
K _s	2	0.126	0.038	0.053–0.200	0.001	2.133	0.144	53.109
P _s	2	0.188	0.078	0.036–0.341	0.016	3.855	0.050	74.059
Mg _s	2	0.206	0.019	0.168–0.244	0.000	0.672	0.412	0.000

'm' and 's' subscripts indicated the concentrations of the minerals in milk and serum, respectively.

Milk Ca



Milk K

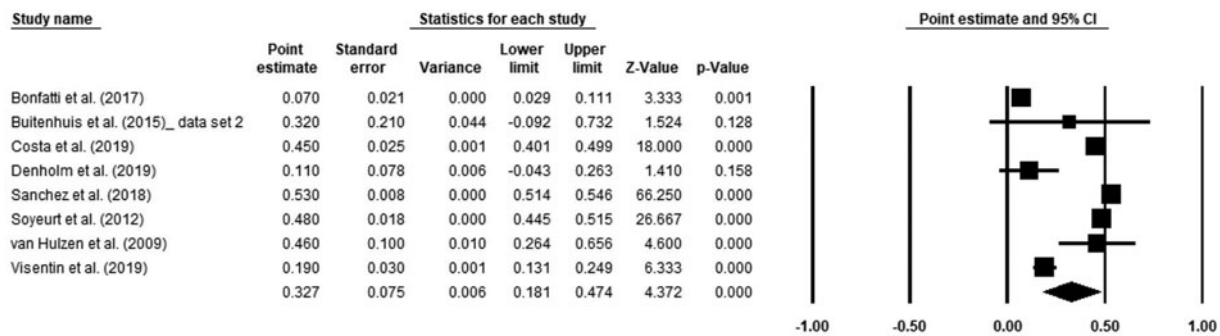
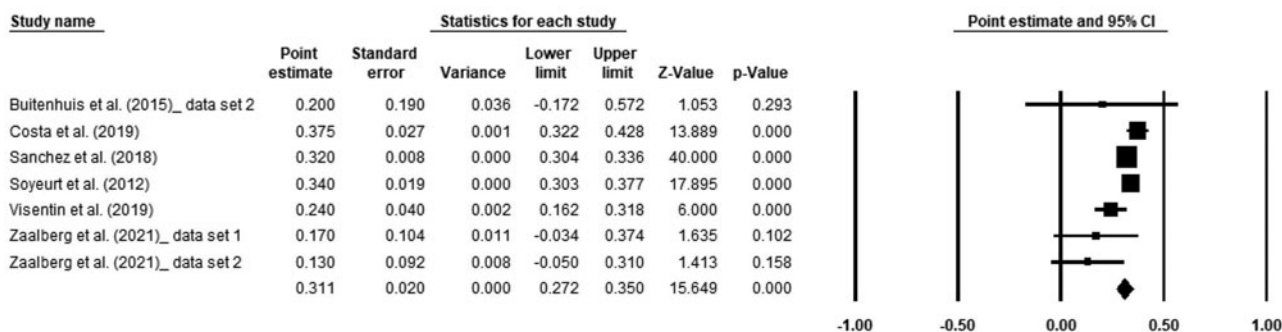


Fig. 1. The forest plots of individual studies and the overall outcome (last line) for heritability estimates of Ca_m and K_m in dairy cows. The mean effect size, calculated according to a random-effects model, is indicated by the diamond at the bottom of each plot. The size of the squares illustrates the weight of each study relative to the mean effect size. Smaller squares represent less weight. The horizontal bars represent the 95% confidence intervals for the study.

Milk Na



Milk P

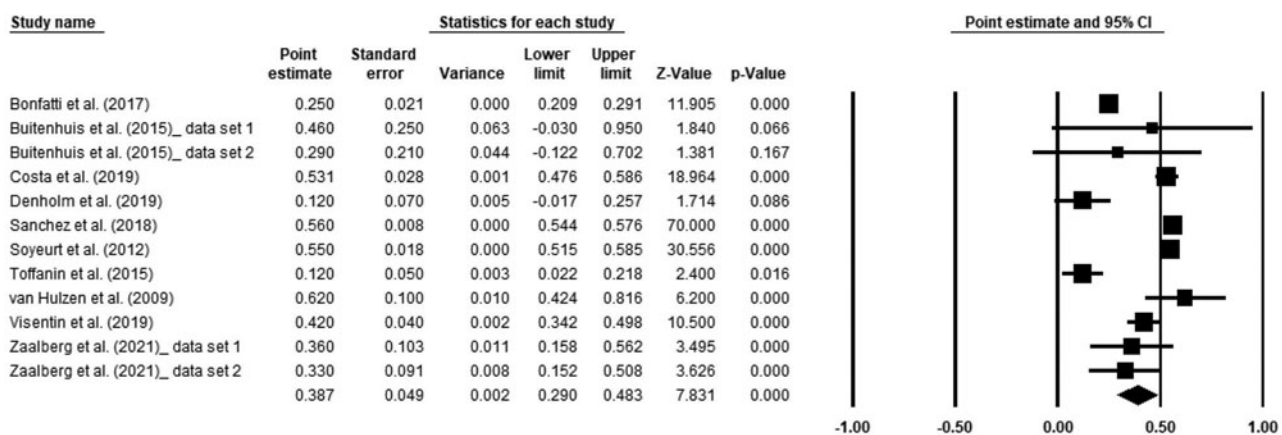


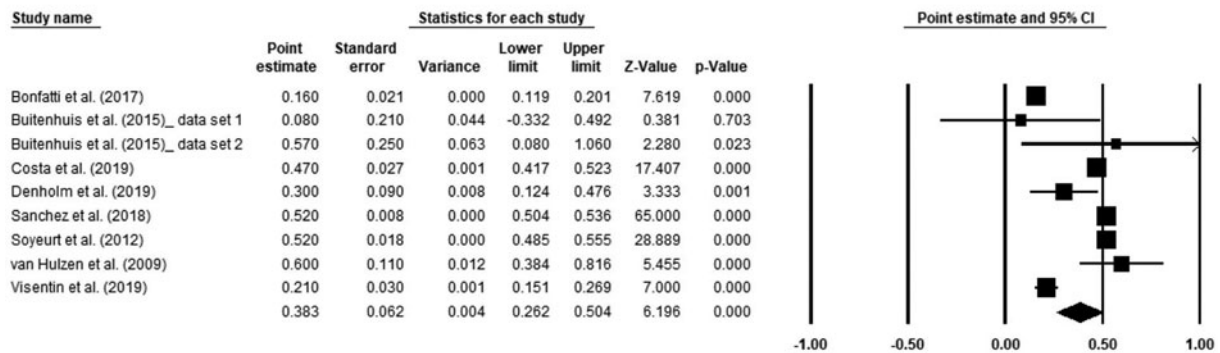
Fig. 2. The forest plots of individual studies and the overall outcome (last line) for heritability estimates of Na_m and P_m in dairy cows. The mean effect size, calculated according to a random-effects model, is indicated by the diamond at the bottom of each plot. The size of the squares illustrates the weight of each study relative to the mean effect size. Smaller squares represent less weight. The horizontal bars represent the 95% confidence intervals for the study.

measured in milk had greater heritability than their counterparts in the serum of dairy cows. In general, most heritability estimates had low standard errors and their 95% confidence intervals were narrow. The heritability estimates for Fe_m and Cu_m were not significant ($P > 0.05$), and their 95% confidence interval included zero. Therefore, the heritability estimates for these two micro-minerals of milk would be considered as zero. The test of the heterogeneity of heritability estimates, performed by *Q* statistics, indicated that except for Se_m ($P = 0.940$), Zn_m ($P = 0.477$), Cu_m ($P = 0.340$), Fe_m ($P = 0.765$), Mn_m ($P = 0.954$), Ca_s ($P = 0.131$), K_s ($P = 0.144$), and Mg_s ($P = 0.412$), which had low *Q* values and non-significant heterogeneity, other minerals showed significant heterogeneities ($P < 0.10$). Consistent with the results obtained by *Q* statistics, the values of the *I*² index indicated the negligible heterogeneity for the heritability estimates of Se_m, Zn_m, Cu_m, Fe_m, Mn_m, and Mg_s, but Ca_s and K_s showed moderate heterogeneities and the other minerals experienced considerable heterogeneities (Table 2). Testing for the occurrence of possible publication bias is not appropriate for the heritability estimates that showed heterogeneity because it could lead to false-positive claims, but the results of Egger's test showed no publication bias for Se_m, Zn_m, and Fe_m (online Supplementary Table S2). Despite the no heterogeneous estimates of heritability for Cu_m,

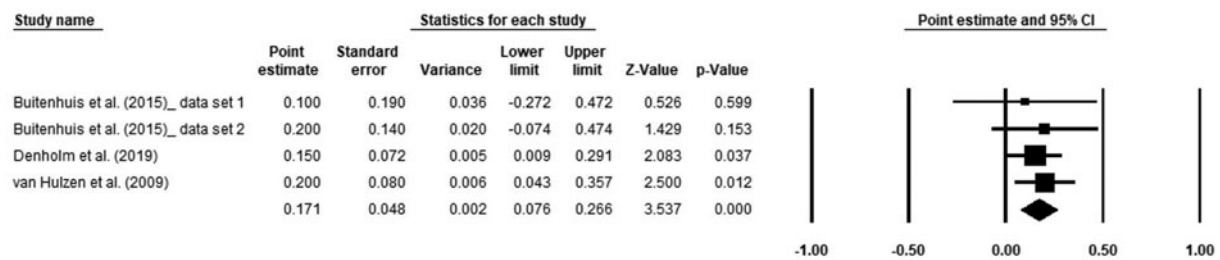
Mn_m, Mg_s, Ca_s, and K_s, Egger's test did not provide any output for these minerals because the average standard error of estimates obtained by random-model was very low.

The forest plots of individual studies and the overall outcome for heritability estimates of milk minerals are presented in Figures 1 to 4. Also, the forest plots of individual studies and the overall outcome for heritability estimates of serum minerals are depicted in online Supplementary Figures S1 and S2. Estimated effect sizes along with their 95% CI were visually displayed in these plots. The heterogeneity of heritability estimates for the majority of minerals was visually evident in forest plots. Funnel plot of mean heritability estimates for milk selenium is shown in Figure 5. The funnel plots of mean heritability estimates for Zn_m, and Fe_m are shown in online Supplementary Figures S3 and S4. Results from statistical tests to evaluate publication bias and the trim-and-fill method to correct funnel plot asymmetry in mean heritability estimates of minerals that did not present heterogeneity are shown in Table 3. Although Egger's test did not detect any bias ($P > 0.10$) with mean heritability estimates for Se_m, Zn_m, and Fe_m, two missing studies were needed at the left side of the funnel plot for Zn_m to regain funnel plot asymmetry according to the trim-and-fill method (online Supplementary Table S2 and Fig. S3).

Milk Mg



Milk Se



Milk Zn

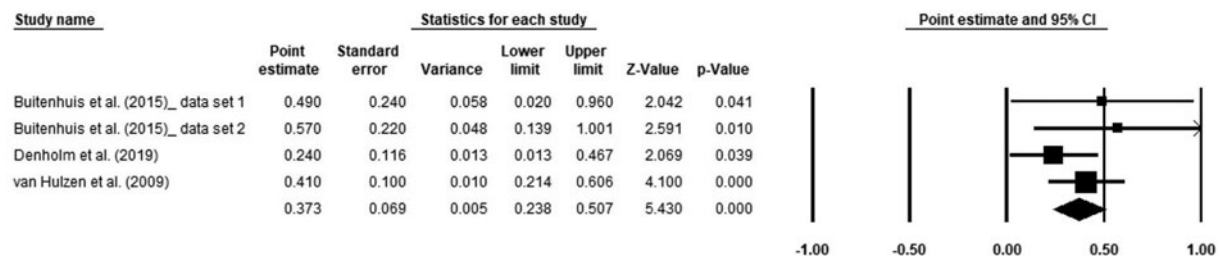


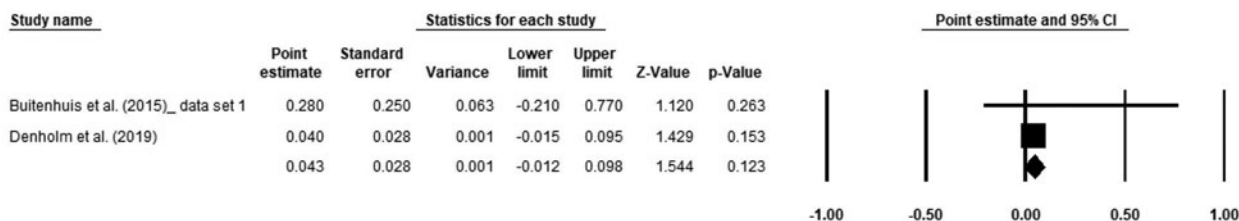
Fig. 3. The forest plot of individual studies and the overall outcome (last line) for heritability estimates of Mg_m , Se_m and Zn_m in dairy cows. The mean effect size, calculated according to a random-effects model, is indicated by the diamond at the bottom of each plot. The size of the squares illustrates the weight of each study relative to the mean effect size. Smaller squares represent less weight. The horizontal bars represent the 95% confidence intervals for the study.

Genetic correlation estimates

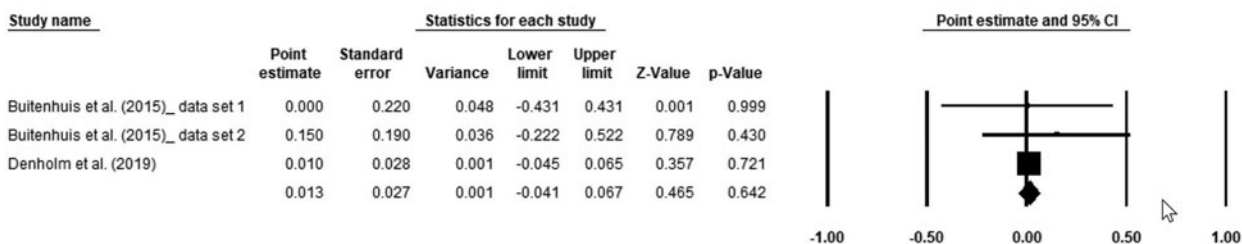
Effect size and heterogeneity of the genetic correlation estimates (based on Q and I^2 statistics) between milk macro-minerals, and between Ca_m and P_m with milk yield in dairy cows obtained from the random-effects model of the meta-analysis are presented in Table 3. The estimates of genetic correlation between milk macro-minerals varied from weak to strong. The weakest genetic correlations observed between Na_m - Mg_m (-0.015) and Na_m - K_m (-0.024), but the strongest genetic correlations were between Ca_m - P_m (0.500), Ca_m - Mg_m (0.510), and Mg_m - P_m (0.625). All estimates of genetic correlation between Na_m with other milk minerals were negative (Table 3). Except for genetic correlations between Ca_m - Na_m , Ca_m - K_m , Na_m - Mg_m , and Na_m - K_m , other correlations were significant and statistically different from zero ($P < 0.05$). The 95% confidence interval of genetic correlations

between Ca_m - Na_m , Ca_m - K_m , Na_m - Mg_m , and Na_m - K_m included zero. Therefore, zero genetic correlations could be concluded between these minerals. The genetic correlation estimates of Ca_m and P_m with milk yield were negative and significant (-0.171 and -0.211 , respectively; $P < 0.05$). The test of the heterogeneity of correlation estimates, performed by Q statistics, showed that except for the genetic correlations between Ca_m - K_m , Na_m - K_m , and Mg_m - P_m which had lower Q values and non-significant heterogeneity ($P > 0.10$), the genetic correlations between other minerals showed significant heterogeneities ($P < 0.10$). The values of the I^2 index indicated considerable heterogeneities for the genetic correlations between Ca_m - K_m , Na_m - K_m , Na_m - P_m , and Mg_m - P_m , moderate heterogeneities between Ca_m - P_m , Ca_m - Na_m , and Na_m - Mg_m , and negligible heterogeneities between other mineral combinations (Table 3). The test of the heterogeneity of genetic correlation estimates between Ca_m and

Milk Cu



Milk Fe



Milk Mn

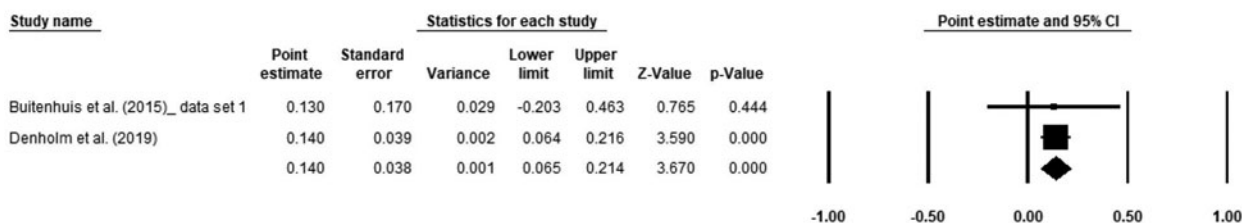


Fig. 4. The forest plot of individual studies and the overall outcome (last line) for heritability estimates of Cu_m, Fe_m and Mn_m in dairy cows. Detailed information is provided in Figure 1.

P_m with milk yield, based on Q and I² statistics, indicated non-significant (P > 0.10) and negligible heterogeneities for these estimates (Table 3).

The forest plots of individual studies and the overall outcome for genetic correlation estimates between milk macro-minerals, and between Ca_m and P_m with milk yield in dairy cows are presented in online Supplementary Figures S5 to S9. The funnel plot of the mean genetic correlation estimate between Ca_m and P_m is shown in online Supplementary Figure S10. Results from statistical tests to evaluate publication bias and the trim-and-fill method to correct funnel plot asymmetry in mean genetic correlation estimates that did not present heterogeneity are shown in online Supplementary Table S3. The results of Egger’s test indicated non-significant (P > 0.10) publication bias for the genetic correlation between Ca_m and P_m. Two missing studies were needed at the left side of the funnel plot for genetic correlation between these two macro-minerals to regain funnel plot asymmetry according to the trim-and-fill method (online Supplementary Table S3).

Discussion

This meta-analysis study evaluated the extent of exploitable genetic variation in milk and serum minerals of dairy cows. This

information is important to assess the possibilities to modify the mineral concentrations of the milk and serum by selective breeding (Buitenhuis *et al.*, 2015). Dairy products, such as milk and cheese, are substantial resources of minerals and contribute greatly to dietary intakes of Ca, P, I, Zn, and Mg (Denholm *et al.*, 2019). Mg and Ca are principally important factors in bone development, especially in children (Givens *et al.*, 2014). Therefore, the circulating concentrations of these minerals in the blood and milk of dairy cows possibly associate with animal fitness given their important functions in several immunological and physiological mechanisms (Alpert, 2017). Ca plays a key role at the start of lactation. Hypocalcaemia is the most important macro-mineral disorder of the transition dairy cow (Tsiamadis *et al.*, 2016). It is connected with health problems including retained fetal membranes, uterine infection, mastitis, ketosis, and displaced abomasum, as well as decreased dry matter intake and milk yield (Tsiamadis *et al.*, 2016). Therefore, recognizing breeding schemes to optimize mineral concentrations for each cow would be of considerable benefit both for the cow and the human dairy product consumer (Denholm *et al.*, 2019).

The lower weighted coefficients of variation indicated the lower dispersion around the weighted means for milk macro-minerals and milk yield among studies which implied the more precise

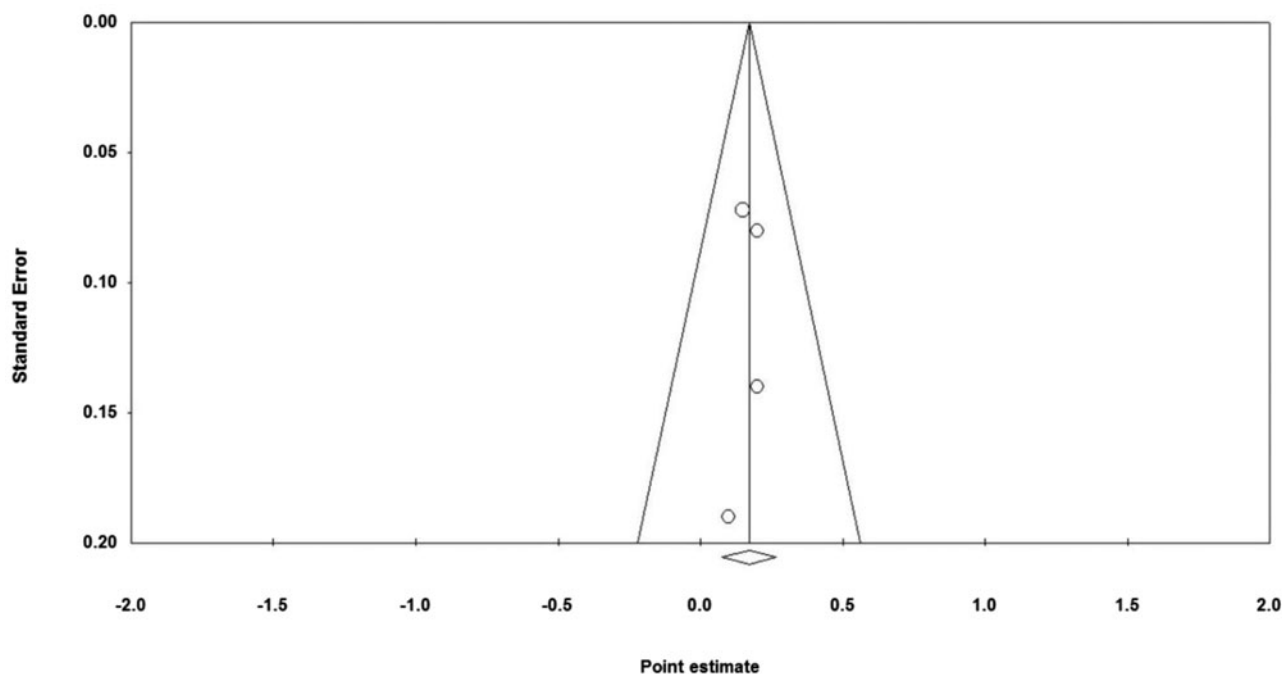


Fig. 5. Funnel plot of mean heritability estimates for Se_m (empty circles). The solid dots are the potentially missing studies imputed from the trim-and-fill method. The open diamond represents the mean and confidence interval of the existing studies and the solid diamond represents the mean and confidence interval if the theoretically imputed studies were included in the meta-analysis.

Table 3. Effect size and heterogeneity of the genetic correlation estimates between milk minerals, and between milk calcium and phosphorus with milk yield in dairy cows obtained from the random-effects model of meta-analysis

Trait 1	Trait 2	N	r_g	95% CI	P -value	Q	P -value	I^2
Ca_m	P_m	3	0.500	0.338–0.634	0.000	3.506	0.173	42.952
Ca_m	Na_m	2	−0.166	−0.357 to 0.038	0.111	1.770	0.183	43.506
Ca_m	Mg_m	2	0.510	0.492–0.527	0.000	0.267	0.605	0.000
Ca_m	K_m	2	−0.236	−0.602 to 0.211	0.299	8.479	0.004	88.206
Na_m	P_m	2	−0.352	−0.589 to −0.059	0.019	2.536	0.111	60.576
Na_m	Mg_m	2	−0.015	−0.221 to 0.193	0.889	2.154	0.142	53.581
Na_m	K_m	2	−0.024	−0.336 to 0.293	0.887	2.748	0.097	63.611
Mg_m	P_m	2	0.625	0.392–0.782	0.000	5.175	0.023	80.678
Mg_m	K_m	2	0.220	0.202–0.237	0.000	0.024	0.878	0.000
P_m	K_m	2	0.129	0.046–0.211	0.002	1.124	0.289	10.993
Ca_m	MY	2	−0.171	−0.236 to −0.104	0.000	0.085	0.770	0.000
P_m	MY	2	−0.211	−0.273 to −0.148	0.000	0.119	0.730	0.000

r_g , Genetic correlation; MY, Milk yield.

'm' subscript indicated the concentrations of the minerals in milk.

estimates of weighted means for these traits. The lowest weighted coefficient of variation was observed for Mg_s (1.16%), showing that its phenotypic variation is restricted biologically. On the other hand, the greatest weighted coefficient of variation was estimated for K_s (82.06%), indicating that there is greater phenotypic variation in this trait than in other traits (de Oliveira *et al.*, 2017).

The standard errors and 95% confidence intervals of the mean heritability estimates for the majority of the minerals in this study were low which indicates that the mean heritability estimates

reported in this study are accurate. The lower heritability estimates observed for serum minerals showed the more evident influence of non-genetic (environmental) factors, but the moderate to high heritability estimates for milk minerals showed a medium-to-high impact of genes with additive action on these traits and possibly a high selection response for them. Although heritability would affect the rate of genetic progress, other variables such as selection intensity, genetic variation and generation interval would also influence the rate in a population of animals.

Because meta-analysis combines published parameter estimates reported by different studies, it is anticipated that the true parameter may differ from study to study (de Oliveira *et al.*, 2017; Ghavi Hossein-Zadeh, 2021). Different studies used in the meta-analysis would be different according to the structure of populations (ie Holstein cows or not, first parity or multiparous cows, repeated records or not, lactation or test-day records, the lactation stage used), source of minerals (ie minerals in milk or serum, mineral contents measured by mid-infrared spectrometry or by prediction equations), analysis model (ie inclusion of random regression or not), data edits and method of analysis (REML or Bayesian).

The greatest genetic correlations were seen between Ca_m with P_m and Mg_m , and between P_m with Mg_m . Also, Na_m had the weakest genetic correlations with Mg_m and K_m . The strong and positive genetic correlations between Ca_m with P_m and Mg_m are the reason for similar genetic and physiological mechanisms controlling these traits. Also, the positive and strong genetic correlation between these traits suggests that selection on Ca_m would improve P_m and Mg_m , resulting in large improvements in milk mineral contents for the advantage of the human dairy consumer. Based on very weak genetic correlation estimates between Na_m with Mg_m and K_m , it would be stated that Na_m did not seem to be genetically associated with these two macro-minerals of milk. The negative genetic correlations of Na_m with other minerals indicated the opposite direction of changes when genetic selection is directly performed on Na_m . These negative genetic correlations would be favorable because the present nutritional guidelines advise decreasing Na ingestion (Whelton and He, 2014). Therefore, if milk mineral concentration is considered as a breeding goal trait, Na should be included as a trait with negative selection pressure to keep it constant, or decrease it (Visentin *et al.*, 2019). Because of the positive and strong genetic correlation between Ca_m with P_m , the negative genetic correlation of these two macro-minerals with milk yield would be expected. The dilution effect would be considered as the possible reason for these negative genetic correlations. The negative genetic correlations of Ca_m and P_m with milk yield can prevent a simultaneous genetic gain for milk yield. This is particularly unfavorable when the payment system is mainly based on the quantity of milk delivered, suggesting milk yield as the main selection objective (Ghavi Hossein-Zadeh, 2021).

Recording new traits will be always an expensive exercise. Therefore, regular recording of the concentration of minerals depends on the capability of dairy cattle breeders to incorporate these new phenotypes in a breeding plan or to apply them as a management help (Ghavi Hossein-Zadeh, 2021). According to the results of the present meta-analysis, enough variability for milk and serum minerals was observed. This implied that these minerals could be modified by genetic selection. From the industry point of view, the delivery of milk appropriate for processing is a pertinent item (Visentin *et al.*, 2019). The participation of stakeholders in the construction of a selection index for milk quality traits, including milk minerals, must be supported in all stages of the process because the quality of milk is not only economically valuable but also is connected with public health problems (Visentin *et al.*, 2019).

In conclusion, the random-effects model meta-analysis performed in this study provided pooled genetic parameter estimates for milk and serum minerals in dairy cows. These estimates are needed for accurate genetic evaluation of dairy cows and the development of an optimum breeding goal. The results of this meta-analysis study showed the existence of additive genetic variation for milk and

serum minerals in dairy cows that could be exploited in genetic selection plans. Improvement in milk minerals could be of benefit for the human nutritional and technological characteristics of milk.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0022029922000127>

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