Genetic analysis of production traits and body size measurements and their relationships with metabolic diseases in German Holstein cattle

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ABSTRACT

This study sheds light on the genetic complexity and interplay of production, body size, and metabolic health in dairy cattle. Phenotypes for body size-related traits from conformation classification (130,166 animals) and production (101,562 animals) of primiparous German Holstein cows were available. Additionally, 21,992, 16,641, and 7,096 animals were from herds with recordings of the metabolic diseases ketosis, displaced abomasum, and milk fever in first, second, and third lactation. Moreover, all animals were genotyped. Heritabilities of traits and genetic correlations between all traits were estimated and GWAS were performed. Heritability was between 0.240 and 0.333 for production and between 0.149 and 0.368 for body size traits. Metabolic diseases were lowly heritable, with estimates ranging from 0.011 to 0.029 in primiparous cows, from 0.008 to 0.031 in second lactation, and from 0.037 to 0.052 in third lactation. Production was found to have negative genetic correlations with body condition score (BCS; −0.279 to −0.343) and udder depth (−0.348 to −0.419). Positive correlations were observed for production and body depth (0.138–0.228), dairy character (DCH) (0.334–0.422), and stature (STAT) (0.084–0.158). In first parity cows, metabolic disease traits were unfavorably correlated with production, with genetic correlations varying from 0.111 to 0.224, implying that higher yielding cows have more metabolic problems. Genetic correlations of disease traits in second and third lactation with production in primiparous cows were low to moderate and in most cases unfavorable. While BCS was negatively correlated with metabolic diseases (−0.255 to −0.470), positive correlations were found between disease traits and DCH (0.269–0.469) as well as STAT (0.172–0.242). Thus, the results indicate that larger and sharper animals with low BCS are more susceptible to metabolic disorders. Genome-wide association studies revealed several significantly associated SNPs for production and conformation traits, confirming previous findings from literature. Moreover, for production and conformation traits, shared significant signals on Bos taurus autosome (BTA) 5 (88.36 Mb) and BTA 6 (86.40 to 87.27 Mb) were found, implying pleiotropy. Additionally, significant SNPs were observed for metabolic diseases on BTA 3, 10, 14, 17, and 26 in first lactation and on BTA 2, 6, 8, 17, and 23 in third lactation. Overall, this study provides important insights into the genetic basis and interrelations of relevant traits in today’s Holstein cattle breeding programs, and findings may help to improve selection decisions.

Key words: body size, conformation traits, metabolic disease, genetic correlation

INTRODUCTION

During the past few decades, gross efficiency of milk production has considerably improved because of increased productivity of animals (Oltenacu and Broom, 2010). Dilution of maintenance, which describes the distribution of a cow’s maintenance requirement to a larger amount of produced milk, has been the main driver of enhanced efficiency so far (Bauman et al., 1985; VandeHaar and St-Pierre, 2006). However, additional productivity improvements in cows are not expected to significantly increase efficiency further (VandeHaar et al., 2016; Guinguina et al., 2020).

Efficiency is determined by the proportion of resources used to produce milk (Bach et al., 2020). From an economic point of view, the most relevant resource in milk production is feed (Connor, 2015; Moallem, 2016). For this reason, improving feed efficiency has recently drawn great attention (Pryce et al., 2014; Hardie et al., 2015; Lovendahl et al., 2018). For direct improvement
of feed efficiency, however, feed intake measurements of individual cows are needed. The lack of such records, as well as the ongoing debate about an appropriate definition of feed efficiency, hinder the implementation of this trait in dairy cattle breeding goals (Hurley et al., 2017; Tempelman and Lu, 2020).

Instead of traits that directly improve feed efficiency, traits that indirectly enhance efficiency of milk production can be considered in breeding goals. Body size and live weight of cows are associated with the maintenance requirement of an animal, which is a major energy sink in dairy cattle (Banos and Coffey, 2012; VandeHaar et al., 2016). For instance, Vallimont et al. (2011) found that body weight and BCS are unfavorably correlated with efficiency traits. Consequently, they concluded that smaller and thinner cows are more efficient compared with larger and heavier animals. The body size of dairy cows has steadily increased in the past few decades, partly owing to selection for milk traits (Pryce et al., 2014; Beavers and Van Doormaal, 2016; VandeHaar et al., 2016). To constrain further increases in body size and thus restrict maintenance feed costs of animals, increasingly more countries include live weight or body size measurements with a negative economic value in their national selection indices (Cole and VanRaden, 2018). Given rising feed prices and other production costs, considering the body size of a cow in breeding goals may become even more important in the future.

Currently, beside efficiency of milk production, animal health and the prevention of production diseases are major concerns in dairy cattle breeding. Particularly in the first weeks after calving, dairy cows are at high risk for metabolic disorders such as ketosis (KET), milk fever (MF), or displaced abomasum (DA). The occurrence of metabolic diseases is tightly linked to the negative energy balance of cows due to an insufficient supply of energy requirements in early lactation (Collard et al., 2000). Previous studies provided evidence that selection for more efficient animals adversely affects their energy balance (Spurlock et al., 2012; Hurley et al., 2018; Seymour et al., 2020). Therefore, it is essential to ensure that selection for efficiency does not exacerbate nutritional deficits in early lactation and further promote the occurrence of metabolic diseases.

Knowledge about the genetic basis of a trait and its genetic correlation with other traits is necessary to adequately incorporate them into breeding objectives. This knowledge allows the prediction of correlated selection response and the avoidance of possible undesirable side effects such as compromised health. Despite the high relevance of this topic, studies investigating the genetic relationships between production, body size measurements of cows, and the occurrence of metabolic diseases in dairy cattle are still lacking. To bridge this gap, the aim of this study was to genetically characterize various traits related to production, body size, and metabolic health in German Holstein cattle, using large-scale representative data sets. Specifically, variance components of traits and genetic correlations between traits were estimated. Additionally, GWAS were carried out to gain a better understanding of the genetic architecture of traits.

MATERIALS AND METHODS

No animals were used in this study, and ethical approval for the use of animals was not necessary.

Animals and Phenotypes

Three data sets were analyzed. Data set (DS) 1 included phenotypes of 130,166 primiparous cows for the 6 conformation traits BCS, body depth (BD), chest width (CW), dairy character (DCH), stature (STAT), and udder depth (UD), which were recorded during routine conformation classification in Germany according to the International Committee for Animal Recording (ICAR) guidelines (ICAR, 2018). Definitions of conformation traits are given in Supplemental Table S1 (http://doi.org/10.5281/zenodo.6874388). Animals were born between January 2013 and December 2018 and originated from 534 farms, with 244 observations per farm on average.

Among the 130,166 cows in DS1, 101,562 animals had phenotypes for the traits milk yield (MKG), fat yield (FKG), and protein yield (PKG) in first lactation (DS2). Production traits were recorded over a lactation length of 280 to 305 DIM. Additionally, milk energy yield (MEY) was calculated according to Nostitz and Mielke (1995) using the following formula:

\[
\text{MEY (MJ)} = 0.802 \times \text{milk yield} + 38.4 \times \text{fat yield} + 23.6 \times \text{protein yield}.
\]

The number of animals, number of observations, and descriptive statistics of all traits in DS1 and DS2 are shown in Table 1.

For some of the farms, records on the metabolic disease traits KET, DA, and MF were available (DS3). Moreover, an additional trait (META) indicating whether an animal had any of the metabolic diseases during lactation (i.e., KET, DA, or MF) was analyzed. Disease traits were recorded by veterinarians and herd managers following the official recording guidelines for health traits (Stock et al., 2013).
were binary coded as 0 (animal had no disease during lactation) or 1 (animal had at least one disease during lactation). Only clinical disease cases were considered, and information on repeated cases of the same disorder during lactation were not available. Data set 3 consisted of 21,992 cows from 33 farms with disease records in first lactation. Phenotypic records for metabolic diseases of 16,641 and 7,096 animals in second and third lactation were available, respectively. Incidences of diseases in first lactation were low, particularly for MF (Table 2). Thus, MF was evaluated only in second and third lactation.

**Precorrection of Phenotypic Data in DS1 and DS2**

Before genetic analyses, raw phenotypes of DS1 and DS2 were adjusted for systematic effects. The precorrection was done separately for the 2 data sets using the following linear models:

**DS1 (conformation):**

\[ y_{ijkl} = \mu + AFC_i + AGE_{j} + DIM_{k} + HYS_{l} + e_{ijkl}, \]

where \( y_{ijkl} \) is the phenotypic observation of each trait (BCS, BD, CW, DCH, STAT, UD), \( \mu \) represents the overall mean, \( AFC_i \) is the fixed effect of age at first calving (5 classes), \( AGE_{j} \) is the fixed effects of age at classification (8 classes), \( DIM_{k} \) is the fixed effect of the days in milk at classification (5 classes), \( HYS_{l} \) represents the fixed effect of the herd-year-season (5,770 levels), and \( e_{ijkl} \) is the random residual effect.

**DS2 (production):**

\[ y_{ijk} = \mu + AFC_i + DIM_j + HYS_k + e_{ijk}, \]

where \( y_{ijk} \) is the phenotypic observation of each trait (MKG, FKG, PKG, MEY), \( \mu \) represents the overall mean, \( AFC_i \) is the fixed effect of the age at first calving, \( DIM_j \) represents the fixed effect of days in milk, \( HYS_k \) is the fixed effect of the herd-year-season (4,521 levels), and \( e_{ijk} \) is the random residual effect.

The statistical precorrection was performed using the `lm()`-function of statistical software R (R Core Team, 2022). For subsequent genetic analyses, residuals of the linear models were used. Owing to the binary coding

**Table 1.** Abbreviations, number of animals (N), and descriptive statistics for studied production and conformation traits in primiparous cows

| Trait               | Abbreviation | N    | Mean  | SD    | Minimum | Maximum |
|---------------------|--------------|------|-------|-------|---------|---------|
| Milk yield, kg      | MKG          | 101,562 | 9,358.7 | 1,593.9 | 3,098.0 | 17,144.0 |
| Fat yield, kg       | FKG          | 101,562 | 362.4  | 56.2   | 110.0   | 625.0   |
| Protein yield, kg   | PKG          | 101,562 | 318.7  | 50.6   | 109.0   | 547.0   |
| Milk energy yield, MJ| MEY          | 101,562 | 28,958.8 | 4,335.8 | 9,549.8 | 47,525.4 |
| Body condition score| BCS          | 133,166 | 5.2    | 1.2    | 1       | 9       |
| Body depth score    | BD           | 133,166 | 6.2    | 1.2    | 1       | 9       |
| Chest width score   | CW           | 133,166 | 5.5    | 1.3    | 1       | 9       |
| Dairy character score| DCH         | 133,166 | 5.8    | 1.3    | 1       | 9       |
| Stature, cm         | STAT         | 133,166 | 150.2  | 3.7    | 120     | 180     |
| Udder depth score   | UD           | 133,166 | 6.1    | 1.2    | 1       | 9       |

**Table 2.** Incidence of diseases\(^1\) defined as the proportion of animals with at least one case of disease during lactation and estimated genomic heritabilities on the observed scale \( h_{\text{obs}}^2 \) and heritabilities transformed to the underlying scale \( h_{\text{und}}^2 \) using the Dempster-Lerner equation (Dempster and Lerner, 1950) in first, second, and third lactation\(^2\)

| Lactation | KET | MF  | DA  | META |
|-----------|-----|-----|-----|------|
| First     | 1.15| 0.08| 0.78| 1.82 |
| h\(_{\text{obs}}^2\) | 0.011 (0.003) | — | 0.029 (0.005) | 0.019 (0.004) |
| h\(_{\text{und}}^2\) | 0.138 (0.038) | — | 0.488 (0.084) | 0.170 (0.036) |
| Second    | 3.39| 0.92| 1.66| 4.62 |
| h\(_{\text{obs}}^2\) | 0.027 (0.005) | 0.008 (0.004) | 0.030 (0.006) | 0.031 (0.006) |
| h\(_{\text{und}}^2\) | 0.156 (0.029) | 0.119 (0.059) | 0.287 (0.057) | 0.146 (0.028) |
| Third     | 6.48| 4.04| 3.15| 9.45 |
| h\(_{\text{obs}}^2\) | 0.052 (0.010) | 0.047 (0.009) | 0.037 (0.009) | 0.049 (0.010) |
| h\(_{\text{und}}^2\) | 0.197 (0.038) | 0.241 (0.046) | 0.225 (0.055) | 0.148 (0.030) |

\(^1\)DA = displaced abomasum; KET = ketosis; MF = milk fever; META = all metabolic diseases.

\(^2\)Values in parentheses are standard errors.
of disease traits in DS3, correction for fixed effects was done during genetic analyses.

**Genotypes and Quality Control**

From routine genetic evaluation, genotypes (45,613 SNPs) were available for all 130,166 animals with phenotypic observations. For further analysis, only genetic variants on autosomes were considered. Quality control of data was carried out using PLINK v1.09 (Purcell et al., 2007). Single nucleotide polymorphisms with a minor allele frequency lower than 1% and SNPs with a deviation from Hardy-Weinberg equilibrium at a threshold of \( P < 1 \times 10^{-5} \) were removed. After quality control, a final data set including 130,166 animals and 44,144 SNPs remained.

**Variance Components and Genetic Correlations**

Genetic and residual variances for traits in DS1 and DS2 were estimated with genome-based restricted maximum likelihood implemented in the software GCTA (Yang et al., 2011), using the following model:

\[ y = \mathbf{1}_n \mu + Zg + \mathbf{e}, \]

where \( y \) is a vector of preadjusted phenotypic records for production or conformation traits, \( \mathbf{1}_n \) is a vector of ones, \( \mu \) is the overall mean, \( Z \) is a design matrix, and \( g \) is the vector of additive genetic effects distributed \( g \sim N(0, \mathbf{G} \sigma_g^2) \), where \( \mathbf{G} \) represents the genomic relationship matrix and \( \sigma_g^2 \) is the additive genetic variance. Further, \( \mathbf{e} \) is a vector including the random residual terms distributed as \( \mathbf{e} \sim N(0, \mathbf{I} \sigma_e^2) \), where \( \mathbf{I} \) is an identity matrix and \( \sigma_e^2 \) is the residual variance. To estimate heritabilities of binary disease traits in DS3, the linear model was extended by a vector and the respective design matrix containing the fixed effects age at first calving (5 classes) and herd-year-season (427, 357, and 235 levels for first, second, and third parity, respectively). Additionally, estimated heritabilities of binary disease traits on the observed scale were transformed to the underlying scale using the equation from Dempster and Lerner (1950).

For estimation of genetic correlations between production and conformation traits, bivariate models for pairwise combinations of all preadjusted phenotypes were used in the same manner as described above. Similarly, genetic correlations between metabolic diseases and other traits were estimated. Fixed effects were included in the model depending on the combination of traits studied.

**Genome-Wide Association Studies**

Single-trait GWAS for each phenotype were performed using GCTA and the following single SNP regression mixed linear model:

\[ y = \mathbf{1}_n \mu + Zg + Wv + \mathbf{e}, \]

where \( y \) is the vector of preadjusted phenotypes (production or conformation traits); \( \mathbf{1}_n \) is a vector of ones; \( \mu \) is the overall mean; \( g \) is the vector of polygenic effects with \( g \sim N(0, \mathbf{G} \sigma_g^2) \), where \( \mathbf{G} \) represents the genomic relationship matrix and \( \sigma_g^2 \) is the polygenic additive genetic variance; \( v \) is the vector of SNP effects; and \( \mathbf{e} \) is the vector of random residuals. \( Z \) and \( W \) are incidence matrices for \( g \) and \( v \), respectively. For binary disease traits, the model was extended by the fixed effects age at first calving-class and herd-year-season.

Genetic variants were considered to be significantly associated with the trait of interest at a Bonferroni-corrected threshold of \( P < 1.13 \times 10^{-6} \) \([0.05/44,144]\), \(-\log_{10}(P) \approx 5.95\). For GWAS of disease traits, a further less conservative threshold for suggestive associations was set to \( P < 2.27 \times 10^{-5} \) \([1/44,144]\), \(-\log_{10}(P) \approx 4.64\). To assess model quality, quantile-quantile plots were visually inspected to compare the observed and expected distributions of \(-\log_{10}(P)\) under the assumption of no association. Additionally, genomic inflation factors \( \lambda \) (Devlin and Roeder, 1999) were computed.

**RESULTS**

**Variance Components and Correlations**

Variance components and genomic heritabilities of production and conformation traits are shown in Table 3. The heritability of production traits in first lactation was 0.333 (±0.012) for MKG, 0.279 (±0.012) for FKG, and 0.240 (±0.011) for PKG and MEY. The heritability of conformation traits was lowest for CW (0.149 ± 0.010) and highest for STAT (0.368 ± 0.020).

Genetic correlations between production traits and conformation traits are presented in Table 4. Regarding production, all traits were highly correlated with each other, showing correlations between 0.538 (±0.020, MKG and FKG) and 0.906 (±0.004, PKG and MEY). Among conformation traits, the highest positive genetic correlation was found for BCS and CW (0.704 ±
The strongest negative correlation was between BCS and DCH ($-0.855 \pm 0.008$). Stature showed low to medium correlations with other conformation traits, and the strongest correlation was with UD ($0.338 \pm 0.019$).

Genetic correlations between production traits and BCS were all negative, ranging from $-0.276 (\pm 0.033$, MKG and BCS) to $-0.343 (\pm 0.021$, MEY and BCS). Similarly, negative genetic correlations were found for production and UD, with correlations varying between $-0.348 (\pm 0.024$, FKG and UD) and $-0.419 (\pm 0.019$, MEY and UD), meaning that cows with deep udders showed higher production. By contrast, positive correlations were observed for production and the conformation traits BD, DCH, and STAT. The strongest positive correlations were identified between production traits and DCH, ranging from $0.334 (\pm 0.019$, MKG and DCH) to $0.422 (\pm 0.020$, MEY and DCH), implying that sharp animals tend to have higher production. Genetic correlations for production and BD varied from $0.138 (\pm 0.022$, MKG and BD) to $0.228 (\pm 0.023$, MEY and BD). Stature had somewhat lower genetic correlations with production traits, with values ranging from $0.084 (\pm 0.020$, FKG and STAT) to $0.158 (\pm 0.021$, PKG and STAT).

In primiparous cows, heritabilities of metabolic diseases on the observed scale were $0.011 (\pm 0.003)$ for KET, $0.029 (\pm 0.005)$ for DA, and $0.017 (\pm 0.004)$ for META (Table 2). In second lactation, heritability estimates varied between $0.008 (\pm 0.004$, MF) and $0.031 (\pm 0.006$, META), whereas in third lactation, the estimate ranged from $0.037 (\pm 0.009$, DA) to $0.052 (\pm 0.010$, KET). After transformation to the underlying scale, approximate heritabilities for metabolic diseases were between $0.119 (\pm 0.059$, MF in second lactation) and $0.488 (\pm 0.084$, DA in first lactation).

Genetic correlations of disease traits KET, DA, and META in first lactation with production and conformation traits are presented in Figure 1 and Supplemental Table S2 (http://doi.org/10.5281/zenodo.6874388). Owing to the low prevalence of MF, correlations between MF and other traits could not be estimated. Other disease traits were positively correlated with production traits, showing correlations from $0.111 (\pm 0.061$, MEY and DA) to $0.224 (\pm 0.057$, PKG and DA). Moderate negative genetic correlations were found between BCS and DCH ($-0.855 \pm 0.008$). Stature showed low to medium correlations with other conformation traits, and the strongest correlation was with UD ($0.338 \pm 0.019$).

### Table 3. Phenotypic variance ($\sigma_p^2$), additive genetic variance ($\sigma_a^2$), residual variance ($\sigma_e^2$), and SNP-based heritability ($h^2$ SNP) of production and conformation traits in first lactation

| Trait | $\sigma_p^2$ | $\sigma_a^2$ | $\sigma_e^2$ | $h^2$ SNP |
|-------|--------------|--------------|--------------|-----------|
| MKG   | 2,386,561.7  (21,765.89) | 795,068.8  (21,530.66) | 1,591,492.8 (11,292.81) | 0.333 (0.01) |
| FKG   | 2,909.4  (25.58) | 811.3  (24.83) | 2,097.5 (14.78) | 0.279 (0.01) |
| PKG   | 2,290.7  (19.55) | 549.5  (18.62) | 1,741.2 (12.24) | 0.240 (0.01) |
| MEY   | 17,018,193.2  (143,684.73) | 4,075,059.4 (136,759.35) | 12,943,133.8 (90,718.48) | 0.240 (0.01) |
| BCS   | 1.52  (0.01) | 0.40  (0.01) | 1.12  (0.01) | 0.263 (0.01) |
| BD    | 1.37  (0.01) | 0.27  (0.01) | 1.10  (0.01) | 0.197 (0.01) |
| CW    | 1.54  (0.01) | 0.23  (0.01) | 1.31  (0.01) | 0.149 (0.01) |
| DCH   | 1.67  (0.01) | 0.42  (0.01) | 1.26  (0.01) | 0.242 (0.01) |
| STAT  | 13.13  (0.13) | 4.83  (0.13) | 8.30  (0.06) | 0.368 (0.02) |
| UD    | 1.33  (0.01) | 0.39  (0.01) | 0.94  (0.01) | 0.293 (0.01) |

1FKG = fat yield; MEY = milk energy yield; MKG = milk yield; PKG = protein yield.
2BD = body depth; CW = chest width; DCH = dairy character; STAT = stature; UD = udder depth.
3Values in parentheses are standard errors.

### Table 4. Genetic correlations between production and conformation traits in first lactation

| Trait | FKG | PKG | MEY | BCS | BD | CW | DCH | STAT | UD |
|-------|-----|-----|-----|-----|----|----|-----|------|----|
| MKG   | 0.538 | 0.878 | 0.833 | $-0.276$ | 0.138 | $-0.012$ | 0.334 | 0.106 | $-0.357$ |
| FKG   | 0.604 | 0.859 | $-0.290$ | 0.224 | $-0.040$ | 0.345 | 0.084 | $-0.348$ |
| PKG   | 0.906 | $-0.278$ | 0.204 | 0.444 | 0.338 | 0.158 | $-0.380$ |
| MEY   | $-0.343$ | 0.228 | $-0.012$ | 0.422 | 0.130 | $-0.419$ |
| BCS   | 0.209 | 0.704 | $-0.855$ | $-0.072$ | 0.166 |
| BD    | 0.620 | 0.422 | 0.130 | $-0.206$ |
| CW    | $-0.498$ | 0.279 | 0.051 |
| DCH   | 0.290 | $-0.125$ | 0.338 |

1FKG = fat yield; MEY = milk energy yield; MKG = milk yield; PKG = protein yield.
2BD = body depth; CW = chest width; DCH = dairy character; STAT = stature; UD = udder depth.
3Standard errors of estimates ranged between 0.011 and 0.030.
and KET (−0.470 ± 0.102), DA (−0.255 ± 0.061), and META (−0.417 ± 0.072), as well as between CW and KET (−0.219 ± 0.103), DA (−0.080 ± 0.072), and META (−0.186 ± 0.081). In contrast, DCH was positively correlated with KET (0.469 ± 0.091), DA (0.269 ± 0.062), and META (0.459 ± 0.072). Genetic correlations between STAT and metabolic diseases were 0.234 (±0.090), 0.172 (±0.061), and 0.242 (±0.073) for KET, DA, and META, respectively. Body depth and UD were weakly correlated with disease traits in first lactation, and estimates were characterized by large standard errors.

Genetic correlations between body size measurements and metabolic disease traits in second lactation are given in Table 5. In general, correlations between traits were less pronounced than in first lactation. However, BD showed moderate correlations with DA (0.309 ± 0.071) and META (0.201 ± 0.072) in second lactation. Clear negative genetic correlations were found for UD and KET (−0.230 ± 0.067), MF (−0.232 ± 0.115), and META (−0.238 ± 0.066) in second lactation. Genetic correlation between STAT and DA (0.240 ± 0.064) was more unfavorable in second than in first lactation. For most trait combinations in third lactation, genetic cor-

Table 5. Genetic correlations between body size measurements\(^1\) from first lactation and metabolic disease traits\(^2\) in second lactation\(^3\)

| Item | KET | DA | MF | META |
|------|-----|----|----|------|
| BCS  | −0.358 (0.070) | −0.142 (0.068) | −0.167 (0.117) | −0.319 (0.068) |
| BD   | 0.077 (0.073)  | 0.309 (0.071)  | 0.068 (0.121)  | 0.201 (0.072)  |
| CW   | −0.188 (0.079) | −0.077 (0.078) | −0.042 (0.129) | −0.109 (0.072) |
| DCH  | 0.273 (0.070)  | 0.212 (0.067)  | 0.178 (0.119)  | 0.346 (0.069)  |
| STAT | 0.167 (0.067)  | 0.240 (0.064)  | −0.141 (0.112) | 0.165 (0.064)  |
| UD   | −0.230 (0.067) | −0.086 (0.067) | −0.232 (0.115) | −0.238 (0.066) |

\(^1\)BD = body depth; CW = chest width; DCH = dairy character; STAT = stature; UD = udder depth.  
\(^2\)DA = displaced abomasum; KET = ketosis; META = all metabolic diseases; MF = milk fever.  
\(^3\)Standard errors in parentheses.
relations were low and estimates were attached to large standard errors due to the small sample size (Table 6).

**Genome-Wide Association Studies**

Quantile-quantile plots and genomic inflation factors for all traits are shown in Supplemental Figure S1 and S2 (http://doi.org/10.5281/zenodo.6874388). Genomic inflation factors were slightly deflated for production traits ($\lambda = 0.93–0.98$) and conformation traits ($\lambda = 0.94–0.98$) but were generally in an acceptable range. For metabolic disease traits in all lactation numbers, genomic inflation factors were close to 1.

**Production Traits.** Figure 2 shows Manhattan plots for production traits MKG, FKG, PKG, and MEY, and Supplemental Table S3 (http://doi.org/10.5281/zenodo.6874388) shows identified SNPs. In GWAS, clear peaks for production traits were found on BTA 3, 5, 6, 11, 14, 19, 20, 27, and 29. On BTA 14, a pronounced peak from 0.49 to 1.85 Mb, including several signals for MKG, FKG, and PKG, was observed with the most significant SNP ARS-BFGL-NGS-4939. Additionally, a strong hit was found on BTA 6 from 85.49 to 87.27 Mb comprising SNPs associated with all production traits. Moreover, several signals were identified on BTA 5 (91.20–94.35 Mb) for FKG and on BTA 20 (29.36–31.91 Mb) for MKG.

**Body Size Traits.** For all conformation traits studied, several SNPs reached the genome-wide significance threshold (Figure 3, Supplemental Table S4, http://doi.org/10.5281/zenodo.6874388). For traits BCS, CW, DCH, and UD, the analysis uncovered marked peaks on BTA 6 from 85.90 to 88.33 Mb. On BTA 5 (88.36 Mb), a shared signal was found between BCS, DCH, and UD. For STAT, hits on various chromosomes (BTA 2, 5, 7, 8, 11, and 19) were observed, with the strongest peaks on BTA 5 (105.35–105.78 Mb) and BTA 11 (78.08–79.41 Mb). Similarly, for UD, various genome-wide significant SNPs were located on BTA 4, 5, 6, 8, 11, and 19.

Interestingly, we detected shared signals for production and conformation traits on BTA 5 (88.36 Mb) and BTA 6 (86.40–87.27 Mb).

**Metabolic Diseases.** Manhattan plots for metabolic disease traits in first and third lactation are given in Figures 4 and 5, and significant SNPs are presented in Supplemental Tables S5 and S6 (http://doi.org/10.5281/zenodo.6874388).

For disease traits in first lactation, only one SNP for DA (BTA10, 18.25 Mb) reached the Bonferroni-corrected threshold. Two more SNPs on BTA 3 (111.68 Mb) and BTA 26 (123.69 Mb) were significant for DA at the suggestive threshold. For META, signals at the suggestive level were found on BTA 14 (26.89 Mb) and BTA 17 (28.95 Mb). For KET, none of the SNPs reached significance in first lactation.

Similarly, no associated loci were detected for metabolic disease traits in second lactation (Supplemental Figure S3, http://doi.org/10.5281/zenodo.6874388). In third lactation, however, SNPs on BTA 2, 6, 8, 17, and 23 were identified (Figure 5 and Supplemental Table S6, http://doi.org/10.5281/zenodo.6874388). For KET, 2 SNPs were located on BTA 2 (71.44 Mb, 84.97 Mb). Additionally, 3 variants were found for KET on BTA 8 in the genomic region from 4.42 Mb to 4.66 Mb. For META, 3 significantly associated genetic variants were observed on BTA 6 at 86.92 Mb. Additionally, for MF, SNPs on BTA 17 and 23 were above the suggestive threshold.

**DISCUSSION**

**Heritabilities**

Heritabilities for production and most conformation traits were in agreement with findings from previous studies (Van Dorp et al., 1998; Dechow et al., 2004; Kadarmideen, 2004; Stoop et al., 2008; Dadpasand et al., 2012; Mehtio et al., 2021). For STAT, however, several studies reported higher heritabilities in different...
Figure 2. Manhattan plots showing $-\log_{10}(P)$ of GWAS for production traits (lactation yield) milk kilograms (MKG), fat kilograms (FKG), protein kilograms (PKG), and milk energy yield (MEY) in first lactation. The red line indicates the genome-wide threshold at $-\log_{10}(P) = 5.95$. 
Figure 3. Manhattan plots showing $-\log_{10}(P)$ of GWAS for conformation traits BCS, body depth (BD), chest width (CW), dairy character (DCH), stature (STAT), and udder depth (UD). The red line indicates the genome-wide threshold at $-\log_{10}(P) = 5.95$. 
Figure 4. Manhattan plots showing $-\log_{10}(P)$ of GWAS for metabolic disease traits displaced abomasum (DA), ketosis (KET), and all metabolic diseases (META) in first lactation. The red line indicates the genome-wide threshold at $-\log_{10}(P) = 5.95$, and the blue line indicates the suggestive threshold at $-\log_{10}(P) = 4.64$. 

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Figure 5. Manhattan plots showing $-\log_{10}(P)$ of GWAS for metabolic disease traits displaced abomasum (DA), ketosis (KET), milk fever (MF), and all metabolic diseases (META) in third lactation. The red line indicates the genome-wide threshold at $-\log_{10}(P) = 5.95$, and the blue line indicates the suggestive threshold at $-\log_{10}(P) = 4.64$. 
Holstein populations compared with our results, with values ranging between 0.43 and 0.71 (Pérez-Cabal and Alenda, 2002; de Haas et al., 2007; Haile-Mariam et al., 2013; Bilal et al., 2016; Manzanilla-Pech et al., 2016).

Among studies, heritabilities for metabolic disorders are often inconsistent. The main reasons for this inconsistency are heterogeneous data sets with corresponding differences in incidence rates of diseases used for the estimation of genetic parameters and varied statistical models applied (linear vs. threshold models) (Emanuelson, 1988; Zerbin et al., 2015; Pryce et al., 2016). Moreover, Gianola (1982) demonstrated that heritability estimates are influenced by disease frequency when linear models are used for binary traits, which exacerbates the difficulty in comparing results across studies.

Similar to our study, Koeck et al. (2013) applied linear models and found low heritabilities for DA (0.04 ± 0.005) and KET (0.02 ± 0.006) in primiparous cows. Using threshold methodology, Parker Gaddis et al. (2014) reported higher estimates of 0.22 ± 0.03 for DA and 0.09 ± 0.02 for KET in first lactation. The transformed heritabilities on the underlying scale in our study were much higher for DA (0.488 ± 0.084) but similar for KET (0.138 ± 0.038). The high estimate for DA was likely because of the low incidence of disease (Stock et al., 2005).

For MF, our results revealed heritabilities on the observed scale of 0.008 (±0.004) and 0.047 (±0.009) in second and third lactation, respectively. Koeck et al. (2015) found a low heritability of 0.011 (0.003) for MF in second to fifth parity estimated by linear models. The study of Saborío-Montero et al. (2018) observed a heritability of 0.03 (±0.002) for MF, which was calculated with a linear animal model. By contrast, Heringstad et al. (2005) estimated heritabilities of 0.09 (±0.02), 0.11 (±0.01), and 0.13 (±0.01) in first, second, and third lactation, respectively, for MF in Norwegian Red cattle, using a threshold model. These results corresponded with our approximated heritability on the underlying scale for MF in second lactation (0.119 ± 0.059). In third lactation, however, our study revealed a considerably higher estimate on the underlying scale (0.241 ± 0.046).

Collectively, the results clearly showed that metabolic diseases are generally heritable, although only to a lower degree. In many countries, metabolic disease traits are already considered in national selection indices. However, reliabilities of genomic breeding values are yet rather low. Therefore, continuous data recording of metabolic disease traits is essential to estimate more accurate breeding values and thereby improve genetic progress in metabolic health of dairy cows.

In the present study, only clinical cases of metabolic disorders were recorded and analyzed. Particularly for MF, however, undetected subclinical cases of disease are expected to be much more frequent than clinical cases with visible symptoms. According to Reinhardt et al. (2011), subclinical hypocalcemia occurs in up to 50% of cows, depending on parity number. A similar situation occurs for ketosis, with subclinical cases appearing at high frequency and causing substantial economic losses in dairy cattle (Mostert et al., 2018; Steeneveld et al., 2020).

**Genetic Correlations**

**Production and Body Size.** The results of our study revealed low to moderate positive genetic correlations of production with STAT and DCH. Wasana et al. (2015) observed similar genetic correlations for STAT with MKG (0.12) and PKG (0.14) in first-parity cows. Ahlborn and Demple (1992) reported higher genetic correlations between STAT and MKG (0.34 ± 0.105) and between FKG (0.25 ± 0.112) and PKG (0.32 ± 0.107) in primiparous Holstein Friesian cattle. From the literature, DCH is known to have a much stronger positive correlation with production yield than STAT (Hansen et al., 2002; Lassen et al., 2003), which corresponds to our findings.

The correlations for STAT and DCH with production imply that larger and sharper animals tend to have higher yield, which is well known. However, the body size of cows is not only related to milk production but also to feed intake. Manzanilla-Pech et al. (2016) reported considerable genetic correlations for DMI with STAT (0.57 ± 0.11), CW (0.61 ± 0.13), BD (0.49 ± 0.12), and BCS (0.46 ± 0.15) in US Holstein cows. In line with that, Manafiazar et al. (2016) demonstrated significant genetic correlations for DMI and BD (0.44 ± 0.09), CW (0.68 ± 0.08), and STAT (0.45 ± 0.09), clearly indicating that larger cows consume more feed. The same study also revealed an antagonistic genetic relationship between STAT and gross energy efficiency (−0.32 ± 0.20). A similar tendency was found for BCS by Vallimont et al. (2011). They investigated strong unfavorable genetic correlations between different efficiency parameters and BCS (−0.64 ± 0.17 to −0.70 ± 0.16) in dairy cattle. In accordance with that, cattle breeds of smaller body size such as Jersey have been demonstrated to generally exhibit better production efficiency than the larger Holstein Friesian breed (Prendiville et al., 2009; Lembeye et al., 2016). Even though production efficiency of dairy cattle has improved significantly because of higher production, benefits seem to be partly cancelled by higher feed intake. Consequently, results from our study and those in the literature suggest that larger cows generally have higher production levels, but not necessarily better efficiency.
Beside the efficiency aspect, the environmental impact, in particular the carbon footprint of milk production, is becoming increasingly relevant. Zetouni et al. (2018) analyzed genetic relationships of conformation traits and CH4 emissions and showed negative genetic correlations between CH4 and BCS (−0.28 ± 0.10) and CW (−0.20 ± 0.13), implying that larger animals produce less CH4. A different picture was revealed by Manzanilla-Pech et al. (2021), who observed a strong positive genetic correlation between CH4 and body weight (0.65 ± 0.07), suggesting that heavier animals have higher CH4 production. These findings are supported by the study from López-Paredes et al. (2020) that demonstrated positive genetic correlations between CH4 and STAT (0.43), CW (0.26), and BCS (0.09). However, Breider et al. (2019) found no significant genetic correlations for CH4 and body weight in dairy cattle. Based on these inconsistent results, it becomes apparent that further research in this area is needed to verify genetic relationships between CH4 and conformation traits.

Production, Body Size, and Metabolic Diseases. All genetic correlations between production traits and metabolic diseases in first lactation were positive and low to moderate, indicating that higher producing cows are more susceptible to metabolic disorders. Although the genetic associations between production and metabolic health are of high importance, current research investigating them is still limited. Parker Gaddis et al. (2014) reported genetic correlations close to 0 (0.02 ± 0.017) between milk yield and both DA and KET in first parity cows. Similarly, Koeck et al. (2013) demonstrated that milk yield in early lactation was genetically uncorrelated with DA and KET. In line with our results, Harder et al. (2006) computed genetic correlations between metabolic diseases and persistency of production traits in German Holstein cattle, with values ranging from 0.10 to 0.19, which points out antagonistic relationships between health and production.

Metabolic diseases typically occur in the first weeks after calving. During this period, the cow faces physiological challenges, such as a pronounced energy deficit due to the imbalance of energy demand for production and energy supply from feed intake. According to Sundrum (2015), the duration and intensity of this imbalance is influenced by the level of milk production. High-yielding cows have greater difficulties with the required metabolic adaptions during early lactation, making them more susceptible to metabolic diseases (van Knegsel et al., 2014; Gross and Bruckmaier, 2019). Collectively, the unfavorable genetic associations between production and metabolic diseases revealed in our study suggest that continued intensive selection for milk yield is likely to exacerbate this situation, leading to negative consequences for the metabolic health of dairy cows.

In the current study, BCS was negatively correlated with KET, DA and META indicating that animals with greater BCS show lower diseases susceptibility. By contrast, DCH showed positive genetic correlations with disease traits, meaning that sharper animals are at higher risk for disease occurrence probably partly caused by higher production levels. These results are in good agreement with findings from previous research. Dechow et al. (2004) reported genetic correlations of −0.48 (0.15) for BCS and DA and 0.65 (0.16) for dairy form and DA. Likewise, in Canadian Holstein cattle, an average genetic correlation between BCS and metabolic diseases of −0.438 (±0.125) was found (Loker et al., 2012). Lassen et al. (2003) obtained genetic relationships of −0.22 ± 0.10 and 0.43 ± 0.09 between digestive diseases (including KET, DA and MF) and BCS and DCH, respectively. According to the authors, the rather weak genetic correlation between BCS and diseases was due to the low disease incidence in first-parity cows.

The association between specific conformation traits and metabolic health of animals is not surprising because BCS and DCH are proxies for the energetic status of animals (Veerkamp and Brotherstone, 1997). Thin cows with limited amounts of energy reserves (i.e., animals with low BCS or high scores for DCH) cannot heavily rely on body tissue mobilization to supply the energy demands in early lactation. Consequently, those animals may go through a prolonged and more extreme negative energy balance, which leads to compromised metabolic health (Collard et al., 2000; Soares et al., 2021).

With exception of MF, STAT was positively correlated with metabolic diseases, with the magnitude of genetic correlations decreasing from first to third lactation. These results demonstrate that cows of larger body size tend to have lower metabolic health, possibly driven by higher production performance. Becker et al. (2012) compared health care costs of Holstein cows selected for either small or large body size. They found significantly greater health costs in first and second lactation for larger animals owing to the higher incidence rates of diseases. Aside from metabolic diseases, Schöpke et al. (2013) showed that animals with an intermediate body size and body weight had the least problems with claw and leg diseases. Overall, cattle with smaller body dimensions seem to show lower occurrence of diseases and thus better health stability.

Genome-Wide Associations

We performed GWAS using a large-scale and representative data set for German Holstein cattle, and
the results revealed many significant signals in different genomic regions. However, the SNP array that was used had a limited marker density and did not allow for a reliable candidate gene analysis. Therefore, detected signals are described here, and potential candidate genes that have previously been reported in literature are discussed.

For production traits, GWAS revealed several significant variants. As expected, a marked hit was observed on BTA 14 in the genomic region from 0.49 to 1.85 Mb, which is known for a high gene content and its association with milk production phenotypes in dairy cattle (Clancey et al., 2019). Beside DGAT1 with its major effect on milk yield (Grisart et al., 2004; Winter et al., 2002), previous studies identified VPS28 as potential candidate loci in this genomic region for milk, fat, and protein yield (Cole et al., 2011; Liu and Zhang, 2019). Likewise, Pedrosa et al. (2021) found VPS28 as well as PLEC and MAF1 in the same genomic area strongly affected milk traits in dairy cattle.

Our study discovered several significant signals for conformation traits harboring many prominent genes that have already been reported in the literature. Cole et al. (2011) identified OSR1 on BTA 11 as a candidate gene for STAT, which coincides with our findings. Significant variants for STAT were found between 105.35 and 105.78 Mb on BTA 5 in our study. A recent study from Doyle at al. (2020) detected the gene NDUFA9, which has an effect on STAT in Holstein Friesian cattle, in that genomic region. In close proximity, CCND2 has been confirmed as a candidate gene for STAT (Abo-Ismail et al., 2017; Bouwman et al., 2018; Jiang et al., 2019). Bouwman et al. (2018) additionally found GHR on BTA 20 affecting STAT. In the genomic region harboring GHR, we found a clear signal for MKG. In accordance with that, a major effect of GHR on milk yield was previously reported by Blott et al. (2003). Thus, results suggest pleiotropic effects of GHR for production and STAT. On BTA 5, we found an additional significant SNP for STAT at 47.85 Mb. Pryce et al. (2011) reported HMGA2 as potential candidate gene for STAT in cattle near that site. This gene has also been shown to be involved in genetic determination of human height (Weedon et al., 2007; Gudbjartsson et al., 2008; Visscher, 2008).

Interestingly, our study uncovered some shared signals for production and conformation traits indicating pleiotropy. On BTA 5 at 88.36 Mb, a clear signal for the traits BCS, DCH, and UD and all production traits was found. Jiang et al. (2019) performed GWAS in US Holsteins based on sequence data and observed pleiotropic effects of gene ABCC9 in that genomic region for production (milk and protein yield) and body-type traits (UD), which confirms our results. Likewise, Nayeri et al. (2016) reported ABCC9 to have effects on fat and protein yield as well as on calving to first service interval in Canadian Holstein cattle.

Moreover, our results showed shared signals for all production and conformation traits BCS, CW, DCH, and UD on BTA 6 between 86.40 and 87.27 Mb. This genomic region was reported to harbor gene NPFRR2 associated with UD in Fleckvieh cattle (Pausch et al., 2016). Furthermore, NPFRR2 was detected as potential candidate loci for clinical mastitis in dairy cattle (Sahana et al., 2014; Wu et al., 2015). Nearby, we identified an additional significant SNP for BCS, DCH, CW, and production trait PKG. In same genomic area, Sodeland et al. (2011) observed gene SLC4A4 as a potential candidate for mastitis susceptibility in Norwegian Red cattle. Pedrosa et al. (2021) detected SLC4A4 as being associated with milk and protein yield in Canadian Holstein cattle. All these results together imply some overlap in genetic determination of production, conformation, and health traits in dairy cattle caused by pleiotropic genes. As most relevant traits in dairy cattle have a complex genomic nature (Hayes et al., 2010; Kemper and Goddard, 2012) and genes are spread throughout the entire genome, genetic overlap across traits is not surprising. However, deeper knowledge on causal genes with pleiotropic effects on different traits may be highly important for prospective breeding.

Few studies have investigated the genetic complexity of metabolic health in dairy cattle. We identified several SNPs for different metabolic diseases, but most of them have not yet been reported in the literature. In primiparous cows, SNP BTB-01948148 on BTA 3 (111.68 Mb) was associated with DA. According to Raschia et al. (2020), this region includes gene CSMD2, which affects milk yield in Holstein cattle. Moreover, a signal for META was found on BTA 17 (28.95 Mb). In close proximity, genes SCLT1 and JADE1 were reported as potential candidate genes for fatty acid composition of milk (Duchemin et al., 2017).

In third-parity cows, clear signals were found for KET on BTA 2 (71.44 and 84.97 Mb). Previously, CFAP221 and HECW2 were identified in these genomic regions as potential candidate loci affecting SCS and milking speed in French Holstein cattle (Marete et al., 2018). A further GWAS hit for KET was found on BTA 8 (4.42 to 4.66 Mb). In the same region, GALNTL6 was identified as a candidate gene in Holstein Friesian for the traits of cull cow carcass weight (Doran et al., 2014), daughter pregnancy rate (Parker Gaddis et al., 2016), and semen quality in Holstein bulls (Borowska et al., 2018).

We identified SNP BTB-00133212 on BTA 6 (86.92 Mb) as being associated with META. In direct proxim-
ity, GC was found as a candidate gene for KET in US Holstein Friesian cattle (Pralle et al., 2020). However, Pacheco et al. (2018) showed that the genomic region containing GC has a substantial effect on the occurrence of MF. These results are not surprising because GC encodes for a vitamin D binding protein and thus possesses a significant role in the regulation of blood calcium concentration in dairy cows (Horst et al., 1994; Cavani et al., 2022).

CONCLUSIONS

This study showed that production is antagonistically correlated with the occurrence of metabolic disorders in dairy cattle and that larger cows tend to have lower metabolic health. Based on these findings, we recommend that more attention be paid to genetic progress in production yield and increase in body size because they are likely to have negative effects on cow health. However, this study also demonstrated that metabolic diseases are heritable, which means that genetic progress through direct selection is possible. In addition, the moderate genetic correlations of metabolic diseases with conformation traits such as BCS or DCH imply that these traits can serve as indicators for metabolic health stability of cows. Therefore, indirect selection could be an additional option to accelerate genetic progress and thereby improve metabolic health in dairy cattle.

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