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Review: Welfare in farm animals from an animal-centred point of view

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ABSTRACT

This review aimed to enlighten aspects of welfare from the farm animal-centred point of view rarely addressed such as those anatomical and physiological alterations induced in farm animals to obtain high performance. Hence, the major working hypothesis was that high-producing farm animals developed an imbalance between body structural and functional capacities and the genetic procedures applied to obtain industrial production of animal protein. This is called "disproportionality", a feature which cannot be compensated by feeding and management approaches. Consequences of disproportionality are the insidious development of disturbances of the metabolism, low-grade systemic inflammation and as a final stage, production diseases, developing throughout the productive life span of a farm animal and affecting animal welfare. Based on scientific evidence from literature, the review discusses disproportional conditions in broilers, laying hens, sows, piglets, dairy cows, bulls and calves as the most important farm animals for production of milk, meat, foetuses and eggs. As a conclusion, farm animal welfare must consider analysing issues from an animal-centered point of view because it seems evident that, due to genetics and management pressures, most of farm animals are already beyond their physiological limitations. Animal welfare from an animal-centered point must be addressed as an ethical step to establish limits to the strength placed on the animal's anatomical and physiological functionality. It may allow more sustainable and efficient farm animal production and the availability of healthy animal-derived protein for human nutrition worldwide.

Implications

Animal products such as milk, meat and eggs are well-accepted sources of protein for human nutrition. To match the actual and coming needs for animal protein worldwide, breeding high-performing farm animals is one of the solutions. However, these farm animals are at risk to suffer from disturbances caused by intensive metabolic stress, affecting animals health. Many improving approaches in breeding, managing and feeding livestock are performed, but incidence of disturbances is still high. Based on scientific evidence, this paper elucidates that the concert of organ functions is no longer harmonically balanced in high-performing farm animals, thereby reducing animal welfare.

Introduction

The necessary parallelism between curves reflecting the growth of human population and food production has been a long-term argument to promote a constant increase of productive performance in farm animals under intensive systems of production. However, every time, the requested high performance under these systems of production is contrasted with the "Five Freedoms" proposed within the animal rights (UNESCO, 1978), a clear conflict with welfare appears creating a debate that reach practical, scientific and public spaces. Nevertheless, to current knowledge, the imbalance between the high production, induced by genetics and management, and the anatomical and physiological features of farm animals remain poorly explored. However, under intensive production systems, the health and welfare of domestic animals are questionable from anatomical, physiological and behavioural point of view. Hence, ethical discussions are becoming frequent, although very often weakly or poorly documented at a public level.

Meanwhile, an increasing interest of the scientific community in animal welfare issues can be evidenced by searching literature on "welfare in livestock". Here, a substantial difference in the number of published articles (61 vs 361) can be found in PubMed when comparing the years 2011 and 2023, respectively. These articles contain studies focused on enhancing animal welfare by using selective breeding (Brito et al., 2020), genome editing (Raza et al., 2021), nutrition (Idamokoro et al., 2020), management strategies and precision farming technologies (Berckmans, 2014; Aquilani et al., 2022) with findings of these studies being useful at a variable

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extent. Nevertheless, limitations for applying such findings do exist, either because underlying reasons for the high incidence of production-related diseases may not be easily detected, or because the economic cost of establishing and maintenance of technologies derived from those studies represent an unbearable financial cost for farmers. Moreover, the applicability of those studies may not be convincing due to the still frequent violation of the Five Freedoms stated as the animal rights, and/or the prevalent increasing rates of production-related diseases as for example mortality rate in European fattening pigs and lameness in dairy cows (Berckmans, 2014; Jensen et al., 2022). More examples are shown below according to species-specific cases.

Analysing animal welfare from a population point of view (e.g., the pen, the flock, the herd) might not be the right approach as doing it from an animal point of view, because individual, species-specific anatomical, physiological and behavioural conditions should be considered. Often, animal welfare is addressed in simple terms such as "animals are eating, growing and performing"; however, this is not adequately reflecting health and proper metabolic functions. The individual variability in the response to stressors (e.g., food deprivation, heat stress, social stress) pointed out by Brito et al. (2020) supported the importance to consider individual animal welfare. Thus, an internal disproportionality caused by the imbalance between high performance, induced by genetics and management, and the individual animal's anatomic and physiological capability act as a stressor which is not addressed at all. Fundamentally, the animal is unable to cope with this stressor because disproportionality is genetically fixed and any challenge by external stressors will increase the animal's inability to cope with it. The term "disproportionality", previously described by Huber (2018), will be explained and used accordingly to species in the next sections".

This review aimed to bring into discussion the anatomical-physiological condition known as "disproportionality" (Huber, 2018) driven by genetics, epigenetics and management effects on individual animals. Likewise, the underlying hypothesis for this review is that due to the pressure imposed by genetics procedures, management setting and epigenetics events, animals are forced to develop a high metabolic performance (e.g., high milk production, weaning weight and meat yield, foetuses and eggs) which created an imbalance with body structural and functional capacities. Concomitantly, such high metabolic performance is related to disturbances of early development, immature anatomical structures and diminished functional capacity of tissues and organs that ultimately lead to increased and multiple health risk non-compensable with management, feeding and precision farming.

Disproportionality in fast–growing broilers

Modern broiler chickens exhibit accelerated and disproportional growth due to an increased weight gain. In broilers, weight gain and development have varied consistently in particular body regions and muscles, which originally had a different function (Schmidt-Nielsen, 1971). Because of such disproportional growth, several morphological and physiological disturbances leading to pathologies have occurred in broilers. Fast–growing broilers in chicken meat production gain weight quickly and disproportionately with up to 30% of BW as breast muscle, mainly *Musculus pectoralis major* and *minor*. Theses muscles were physiologically made for wing movement during flying; thus, originally, the muscles consisted of a high proportion of red fibres to enable the endurance performance of flying. Besides, a proper mobility of the keel bone (sternum) is essential for respiration in chicken enabling the ventilation of abdominal air sacs (Schmidt-Nielsen, 1971). In the modern broiler chicken, the huge breast muscles consist mainly of white fibres to enable quick and massive hypertrophic growth which changes structural respiratory mechanics (Lake et al., 2020) and functional biochemical features. White fibres differ in their biochemistry in regard to energy production for movement and growth, respectively. While red fibres depend on oxidative metabolism in mitochondria, white muscle fibres are producing energy from glucose by glycolysis with lactate as end product. Lactate needs to be removed from the white muscle fibre and is then oxidised by red fibres or, after transfer into plasma, by the liver. High lactate concentrations within the cell or in the plasma are causing lactate acidosis.

Modern broilers expressing this disproportional growth are at higher risk to develop pathologies in various body functions and tissue structures. Broilers bred for those large white breast muscles could suffer from myopathies, mostly degenerative myopathies such as white striping (**WS**), wooden breast (**WB**) and spaghetti meat (**SM**) (Petracci and Cavani, 2012; Bailey et al., 2020). The incidences and prevalences for degenerative myopathies were varying worldwide but were alarmingly high. For WB, about 61.9% of breast fillets were affected in a Chinese study with 1 135 fillets (Xing et al., 2020). In a Canadian study, examining 9 250 breast fillets, a prevalence of 36.3% for SM, 11.8% for severe WB and 96% for mild or moderate WB was detected (Che et al., 2022). Also, multiple myopathies can occur in the same breast fillets. In a Lithuanian study examining 54 000 broilers for myopathies, an incidence of 15.7% was found for WB and of 18.2% for WB and WS together (Lebednikaite et al., 2023). The pathophysiology of these myopathies is not yet well described. WB was discussed to be not only a myopathy but also a systemic disturbance of energy metabolism due to inefficient lung and heart functions, organs which are too small for supplying the huge breast muscles with oxygen and for removing metabolic waste efficiently. This disproportionality of the cardiovascular and respiratory systems led to lower oxygen saturation and decreased partial pressure of oxygen in the blood of chicken expressing wooden breast (Lake et al., 2020). Furthermore, the blood pH dropped and carbon dioxide and bicarbonate concentrations increased indicating a systemic acidosis (Lake et al., 2020). This acidosis can be based on lactate (which was not measured in that study) as metabolic acidosis, and can also be based on insufficient cardio-respiratory function as respiratory acidosis. Since wooden breast symptoms can occur within the 1st week of age, the cardio-respiratory disproportionality during growth increases the risk for the formation of the myopathy. As a further pathology derived from disproportional growth, an inadequate pulmonary vascular capacity in broilers is well-known since decades (Wideman et al., 2007; Baghbanzadeh and Decuypere, 2008; Kalmar et al., 2013; Wideman et al., 2013). The vascular capacity of lung vessels is essential for oxygen and carbon dioxide exchange. During growth of a broiler, the heart stroke volume increases from 8 ml/min in a hatchling weighing 40 g to 800 ml/min in a 4 000 g broiler chick within 8 weeks of life. From the right ventricle, the total stroke volume blood flows directly into the lung vessels and finally, into the capillaries contacting the *parabronchi* for gas exchange. However, the total heart and lung size as a percentage of live BW are disproportionally too small to balance metabolic needs during growth (about 10.3 and 9.0%, respectively, measured in selected broiler chickens versus non-selected ones (at those times had selected lines still lower breast muscle weights than nowadays (Havenstein et al., 2003)). Furthermore, the capacity of lung arteries to adapt to higher blood flow is too low due to a broiler-specific physiologically and anatomically limited compliance (elasticity) of vessel walls (Wideman et al., 2013). Consequently, the pulmonary vascular resistance increases with growth, causing right ventricle hypertrophy due to the higher heart muscle work load to pump against the higher vascular resistance. Since the higher cardiac output into only marginally widened ves-

sels increases the velocity of blood flow through lung vessels, the time for diffusion of gases is shortened, and the broiler develops a low oxygen saturation (hypoxaemia) and an increase in carbon dioxide load (hypercapnia) (Olkowski et al., 1999). As mentioned before, low oxygen saturation and a lower blood pH due to the increase in carbon dioxide increased the risk to suffer from myopathies such as wooden breast. Beside myopathies, these broilers could also develop the pulmonary hypertension syndrome associated with ascites and heart failure, leading to sudden death. The incidence for the pulmonary hypertension syndrome world-wide was assessed to be 4.7% and could vary up to 20% in some flocks (Balog et al., 2003). In a UK prevalence study, 1.8–2.4 million broiler chickens per year were affected by ascites (Part et al., 2016), causing not only high economic losses but also strongly diminished animal welfare. The high heritability of ascites susceptibility indicates that breeding for high breast muscle accretion and low food conversion rate (or breast conversion rate (g feed/g breast muscle)) strongly promotes the disproportionality of other body organs and tissues, which are equally important for an optimal high performance.

What are the systemic consequences of cardiopulmonary insufficiency?

Clinical symptoms of broiler production diseases could be WB, ascites and reduced growth performance, as already described. However, myopathies were also correlated with disturbances in bone metabolism and mineralisation resulting in reduced femur diameter and a lower calcium and phosphate content of bones. Concomitantly, the bone marrow was occupied by an enhanced number of adipocytes (de Almeida Mallmann et al., 2019). More adipocytes and ectopic fat depots were also observed in the WB muscle (de Almeida Mallmann et al., 2019); and in general, high growth potential was associated with larger abdominal fat pad weight in broilers even without degenerative myopathies (Zuidhof et al., 2014). Increased adiposity and hypoxemic conditions are associated with metabolic inflammation and oxidative stress in fast−growing broiler chickens as assessed by gene co-expression network and differential gene expression approaches (Gao et al., 2020, Malila et al., 2022); however, the causal relationship between these features is unclear not only in farm animals but also in humans.

As a working hypothesis, for the fast-growing broiler, it could be assessed that hypoxaemia due to cardiopulmonary insufficiency is the starting point, which leads to a steadily stronger decrease in blood oxygen saturation, to hypercapnia and to an acidotic condition. Subsequently, oxidative stress occurs due to dysfunction of mitochondria, which promotes local and systemic metabolic inflammation and an increase in adipose tissue deposition, even in ectopic places. Thus, during growth, the physiological condition transforms into a pathophysiological condition, which increases the risk to suffer from production diseases. The inborn structural and functional features of the cardiopulmonary system of a broiler chicken are only marginally able to match the needs of high breast muscle production – a situation which cannot be corrected by management and feeding approaches. Due to a very new finding published in 2022, the "breast vessel" in broiler breast muscles, it is discussed that the chicken organism tried to compensate for the hypoxic conditions in the muscle. They developed new arterial branches entering the breast muscle from the surface at the cranial part of the breast muscle, which is macroscopically described by consumers as "long thin worm" (Catala-Gregori et al., 2022). Most likely, this abnormal vascularisation of the breast muscle is an indicator for at least the hypoxic stress in the breast muscle of broilers.

Disproportionality in high-performing laying hens

Modern laying hens were selected for a very high laying performance, and thus, the biochemical pathways, necessary to build up one egg per day, were significantly enhanced. Besides a high metabolic efficiency of the laying duct, especially liver and bones are affected as key providers of components for egg yolk and egg shell synthesis, respectively (Walzem et al., 1993, Sinclair et al., 2023). Focusing solely on egg production, this disproportionality in metabolism increased the risk to suffer from several pathologies. With this established high laying performance of the individual hen, the global egg production is estimated to be based on more than 6 billion laying hens with an average annual egg mass production of about 70 million tonnes with an increasing trend (Fan and Wu, 2022). High-performing laying hen strains are characterised by a large number of eggs (300–400 per period, one egg/day). As examples, Lohmann selected leghorn (white) and Lohmann Brown Classic (brown) are two strains, which are used worldwide for egg production. White and brown hens have a final BW of 1.72 kg and 2.05 kg, respectively, and produce an egg mass of up to 29 kg and 26 kg in 100 weeks (within one laying cycle). Mortality rates within the laying period are 8–9%; the company is advertising the robustness, health and vitality of these laying hen strains (https://lohmann-deutschland.de/ legehennenrassen/). These high-performing laying hens produce the 17fold and 13fold, respectively, of their body mass as egg mass during their productive life span, consisting mostly of protein and lipids. This creates a very intense metabolic situation, in which the gastrointestinal tract, the liver and the laying duct are the most important organs. After completing the laying cycle, these hens were called "spent" egg-laying hens, which were disposed as waste, landfilling, by−product or biomaterial for animal and pet food and for compost as fertiliser in the western society (Fan and Wu, 2022). A second use after mould is not a commonly performed strategy in high−performance animal production.

As a consequence of this disproportionality in metabolic demands solely for egg production, the risk to develop disturbances in structural and functional features, especially in liver and bones, is significantly increased, and respective pathologies occur during the productive life span of laying hens. As highly important production diseases, laying hens could suffer from fatty liver haemorrhagic syndrome (**FLHS**) and keel bone fractures (**KBF**) during egg laying period. Although these diseases cause severe disturbances of health and animal welfare, they do not always affect laying performance in the laying hens. Hens are eating, growing and laying as promised by the manufacturer.

What is fatty liver haemorrhagic syndrome and why does it occur?

Fatty liver haemorrhagic syndrome is a well−described pathophysiology of laying hens and well-known since decades (Walzem et al., 1993, Trott et al., 2014, Shini et al., 2019, Anene et al., 2023). Fatty liver haemorrhagic syndrome hens express high−fat content in the liver, enlarged abdominal fat deposition, subcapsular and liver parenchymal haematomas and haemorrhages into the body cave. Livers are pale in colour, fragile and lacking structural integrity (Shini et al., 2019). Years ago, this was only observed in hens with overfeeding (Walzem et al., 1993). The histopathology of the liver was associated with a lack of reticulin fibres, which are major components of the extracellular matrix (Walzem et al., 1993, Trott et al., 2014). Mechanistically, two pathways were suggested, firstly, hepatocytes swollen by intracellular fat deposition destroyed the fibres mechanically; and secondly, oxygen radicals derived from an excessive lipid metabolism promoted the destruction of reticulin fibres (reticulolysis) (Trott

et al., 2014). Lack of stability in the extracellular matrix causes an instability of hepatocyte organisation, most likely leading to functional insufficiency. Sudden death cases of up to 5% of laying hens during one laying cycle could be the consequence of FLHS, especially observed in hens with higher BW due to overfeeding or cage housing (Trott et al., 2014, Shini et al., 2019). Cage housing led to higher BWs in laying hens at the second half of the laying period compared to hens kept in barn or free-range housing (Shini et al., 2019). Since this FLHS can occur in acute, but also in a chronic form, it is called "the silent killer"; promoting factors are feeding, restricted movement, increased production and environmental challenges such as temperature and humidity (Shini et al., 2019). Recently, another aspect of FLHS was detected, individual feed efficiency was associated with FLHS occurrence in laying hens with higher FLHS incidences in low feed efficient laying hens (feed conversion rate 2.39 ± 0.02) versus high feed efficient laying hens (feed conversion rate 1.83 ± 0.02). Low feed efficiency hens expressed a stronger hepatocellular fat deposition, a higher FLHS lesion score and higher thiobarbituric acid reactive substances (=markers of oxidative stress) concentrations in liver (Anene et al., 2023); egg mass performance and egg quality were lower (Anene et al., 2021). The gizzard weight corrected for BW, which was larger in high feed efficient hens compared to low feed efficient hens, was discussed to be the cause of better utilisation of nutrients and energy (Anene et al., 2023). This interrelationship between feed efficiency and FLHS occurrence is a quite important observation. Feed efficiency was varying strongly within the cohort of this study. Intensive feeding of high−performing laying hens as recommended by the management guide of the breeding company provoked individual responses based on disproportional structural features of the gastrointestinal tract such as gizzard size and most likely, also based on differences in metabolic functional features such as oxdative-antioxidative balance. Thus, one and the same feeding (under the same keeping conditions) fits for some hens, but not for all. Hens with lower feed efficiency were overfed depositing fat into the body cave and into the hepatocytes. Subsequently, BW was higher and egg production was lower. Individually, high−producing laying hens with lower feed efficiency are at higher risk to suffer from FLHS and thereby, disturbances of animal welfare.

What are keel bone fractures and why do they occur?

Egg laying, that means one egg every 24 h for at least 300 days, is affecting the mineral metabolism strongly; the start of egg laying at about week 20 of life requires a profound homeorhetic adaptation of calcium and phosphorus fluxes between gastrointestinal tract, bones and laying duct (synonyma: uterus, shell gland) for egg shell production. Egg shell calcification takes mainly place during the night (about 20 h), hens cannot rely on intestinally absorbed calcium, because they do not eat in darkness. For egg shell calcification, they have to rely on calcium from other sources; about 20–40% of the egg shell calcium is derived from bones (Sinclair et al., 2023). A specific structural issue of laying hens is the medullary bone in long bones (especially in legs and wings) rich in hydroxyapatites [$Ca_{10}(PO_4)_6(OH)_2$], which can easily remineralised in times of dietary calcium intake and which is resorbed during egg shell formation in the night under the circadian regulation of parathyroid hormone and vitamin D_3 (Sinclair et al., 2023). If a high-performing hen starts to resorb not only medullary bone but also structural bone material, this results in a progressive loss of structural bones. As a consequence, fragile bones and weak-shelled eggs are occurring, and bones are more susceptible to fractures. This condition is called osteoporosis in laying hens. Osteoporosis is described as a typical production disease of older laying hens, the homeorhetic adaptation of mineral metabolism is no longer properly working. Fracture incidences increase up to 30% due to osteoporosis (Whitehead and Fleming, 2000). Osteoporosis in laying hens was first described in 1955 involved in a syndrome called caged layer fatigue (Couch, 1955). Fractures can occur during laying period, especially in extended productive periods, in dependency on husbandry systems, during transport to slaughter and also after slaughtering, in the carcasses due to the fragile bones. Especially, the latter leads to lower acceptance of processors of spent hens because of bone splinters in the meat (Whitehead and Fleming, 2000). However, even if the fractures occur mainly at the end of the productive life span of laying hens, this risk is a severe animal welfare issue.

However, although osteoporosis is described as the major bone issue in aged laying hens, a very recent study in high-performing laying hens revealed another insight into their bone health when entering the productive life at about week 20 (Huber et al., 2023, unpublished data). Hens were kept on the floor in deep litter equipped with perches and in metabolic units about 4 weeks before slaughter. After slaughter at different ages, the keel bones of laying hens were isolated and evaluated macroscopically and by X-ray examination. A severity of fracture scoring was applied with 1 = no fracture to 5 = several and severe fractures with fragment deviations. Results showed that concomitantly to the onset of egg laying between week 20 and week 30, more and more hens suffered from fractures of the keel bones from week 30 on. Incidences increased from 40–60% (in week 30) to 65–80% (in week 34) and to 85–95% (in weeks 38 and 42). The number and severity of fractures increased from week 30 to week 42. With increased scores, the number of fractures per keel bone also increased, indicating that there was a recurrent event which damaged the bone several times during the first 42 weeks of life. To conclude, single or multiple KBF can occur quite early in the productive life span of laying hens. This observation of KBF in laying hens was also made in many other studies in the last decade (e.g. Eusemann et al., 2018; Hardin et al., 2019, Wei et al., 2019; Toscano et al., 2020; Thofner et al., 2021). This bone health issue in young laying hens is most likely not based on the pathomechanisms described for osteoporosis, which is a proven condition in older high-performing laying hens affecting especially long leg and wing bones.

What impact do have these findings in regard to physiology and health of bones?

The keel bone (*sternum*) of hens is a large flat bone which area is attaching the breast muscles, and it provides a protective structural element at the ventral body side. The keel bone is ventrally enlarged by a long bone structure, called *carina sterni*, which caudal tip is embedded in the soft abdominal wall structures. Body growth of laying hens is completed at about week 34 of age. Furthermore, the secondary ossification of the keel bone starts at about week 6 of life, develops progressively form cranial to caudal and is completed between weeks 33 and 40 of age (Buckner et al., 1949). The modern high-performing laying hen is pushed to start early with egg laying in about week 20 of age due to genetic selection, management and feeding manipulations. Although duration of maturation processes such as ossification of keel bone was studied in older breeds, it can be questioned if the genetic selection for higher egg−laying performance and the subsequent decision to manage these hens for early onset of egg laying created a disproportionality between body tissue maturation and early reproductive performance. If the cranial to caudal ossification of keel bones can only be completed after about 40 weeks of age, this weak bone is predisposed for fractures at all. In addition, if ontogenetic allocation of calcium to the keel bone is not adequate anymore due to the need for egg shell calcification early in life, the ossification will be incomplete or slowed down. The keel bone

remains fragile. This hypothesis about a defective mineralisation of keel bones is confirmed by the finding that the older the hens were at the onset of egg laying, the lower the prevalence of KBF was at the end of lay (Thofner et al., 2021). Any external stressor such as mechanical insults (e.g. cage furnishing, free−range systems), nutritional imbalances (e.g. calcium, phosphorus) or − as a novel hypothesis – even the frequent laying process of large eggs itself will worsen the condition. The latter is supported by the Danish study which found that "the production of heavier eggs resulted in higher KBF prevalence" in a studied cohort of over 4 500 laying hens (Thofner et al., 2021). According to this hypothesis, descriptions of early-in-life KBF in laying hens should be reconsidered in terms of their pathogenesis. Most likely, the early onset of egg laying and production of large eggs overrun the anatomical features of the hen; it is assumed that there is a rising disproportionality between the individual heńs body mass and the increasing size of eggs during laying period (Yi et al., 2014). The egg weight is strongly increasing from the onset of egg laying (about 35 g/egg) to genetically determined egg weight (about 55 g/egg) at week 40 to week 50 of age (Yi et al., 2014). Furthermore, is could be assumed, that in general, the body mass of the hen was not significantly enhanced by breeding approaches, while egg weight and number of eggs were. This disproportionality could lead to the following structural mismatch. The uterus of the laying duct is located dorsally to the gizzard, the firm muscular stomach which enables the mechanical disruption of the ingested food. Ventrally, the gizzard touches the hind part of the keel bone which is not properly mineralised at onset of egg laying. As a consequence, during the laying process, muscular contraction of the laying duct, but also of the abdominal wall is pushing the egg down to the cloaca for laying. At the same time, mechanical forces provoked by a downwards movement of the gizzard (due to the large egg) could act ventrally onto the hind part of the keel bone leading to KBF. Due to the weakness of the keel bone, this might happen several times during the egg−laying period resulting in multiple KBF.

So far, besides in the above-mentioned study in very young laying hens, increasing prevalence of KBF determined by radiographic examination was also found in living hens at 35, 51 and 72 weeks of age (Eusemann et al., 2018). In this study, hen strains with low and high egg−laying performance and in different housing systems were compared. Strain, age and housing systems had only weak effects on an alarming high KBF prevalence. However, cage and cage-free systems showed also different incidences for KBF with higher incidence values in cage-free systems (Hardin et al., 2019). The overall incidence of KBF in laying hens was 15–55% in furnished cages and 30–97% in non-cage systems (reviewed by Hardin et al., 2019, Wei et al., 2019). In furnished cages, incidences rose from 40% at week 37 of age, to 54.4% at week 42 of age and to 62% at week 60 of age (Wei et al., 2021, 2022). Also, more physically active strains could have a higher incidence of KBF due to mechanical damage in furnished cages, even when egg production is low (Wei et al., 2022). However, the commercial strain Hy-line Brown described in this study expressed about 20% of KBF and about 25% deviations of the keel bone, too (Wei et al., 2022). Other studies indicate that commercial strains had higher incidences for KBF than non-commercial and native strains (Candelotto et al., 2017, Kittelsen et al., 2020). Furthermore, non-laying hens (abolished by drugs) and male chickens under the same keeping conditions did not develop any KBF (Toscano et al., 2020), again supporting a close correlation between egg laying performance and occurring of KBF. However, age at first egg, immature bones and physiologically late ossification of the entire keel bone might contribute to the high incidences of KBF (Toscano et al., 2020, Thofner et al., 2021) caused by this disproportionality between body maturity and early high egg performance. Allocation of resources is not able to support both at the same time properly (Huber, 2018). As consequence, KBF altered behaviour inducing a depressive-like condition (Armstrong et al., 2020), reduced egg production and quality (Rufener et al., 2019, Wei et al., 2020) and caused pain, stress and inflammation in laying hens (Nasr et al., 2012, Wei et al., 2019). Therefore, KBF due to whatever reasons as the production disease of laying hens strongly reduce animal welfare.

Disproportionality in hyperprolific sows and their offspring

Modern sows used for piglet production are selected for large litter sizes (hyperprolific sows) (Riddersholm et al., 2021). Large amounts of piglets per sow and respective higher colostrum and milk output postpartum to nourish the offspring is setting a strong burden on the sow. The disproportional focus on reproduction created systemic metabolic and functional disturbances, which negatively affected not only the sow but also the offspring by metabolic imprinting processes (Riddersholm et al., 2021). As a potential key driver, uterine capacity is anatomically too small to ensure a proper development of offspring. Many modern white breeds such as Landrace, Chester and Yorkshire offer hyperprolific sows for the market. Furthermore, the DanBred is known for its high litter size which was associated with the good mothering abilities of these DanBred sows (https://danbred.com/our-dna/) The Danish pig production increased their litter size from 11.8 total born piglets/litter in 1992 to 19.6 total born piglets/litter in 2020 (Riddersholm et al., 2021). However, about 80% of these born piglets are at high risk for early dying. Many piglets from large litters were too weak to survive due to low birth weight and intrauterine growth retardation (**IUGR**; 20–32% of piglets) (Riddersholm et al., 2021). A strong negative relationship between individual birth weight and percentage of preweaning mortality was observed with an exponential increase of losses in piglets (up to 100%) weighing less than 1.11 kg at birth (birth weight threshold) (Feldpausch et al., 2019). The average litter size of the Feldpausch study was 13.2 (obtained from Large White x Landrace and Pietrain dams in USA and Europe; in total studied 4 068 piglets of 394 litters under modern commercial conditions); thus, the litter size was far below the high litter sizes of DanBred. However, 15.2% of the piglets had birth weights below 1.11 kg and represented 34.4% of preweaning mortalities (8.2% preweaning mortality in piglets $\geq$1.11 kg) (Feldpausch et al., 2019). The litter weight variation was from 0.5 to 2.3 kg, a variation, which was confirmed by many other studies in this field (Feldpausch et al., 2019). Examination of genetic traits related to litter size and piglet birth and weaning weight revealed a heritability of 0.10; any increase in litter size worsens the situation with larger numbers of low birth weight and IUGR piglets (Hellbrügge et al., 2008). Risk factors responsible for impaired litter development could be a reduced quality of follicles on the ovary and disturbed embryonal and foetal development. Maternal structural and functional features could imprint the metabolic conditions, and thereby, health, of offspring at any stage of ontogenesis (Barker, 2007).

What are the reasons for this high litter weight variation?

Embryonic and foetal growth depends on an adequate supply of oxygen and nutrients to match the growth and development needs. From an anatomical point of view, the uterus horn length, the vascularisation of the uterus and placenta formation determine the sustentative environment for each foetus. As a further important prerequisite for an optimal foetal growth, the dam needs to be healthy and ingests enough high-quality food and water. Good health and food intake can be ensured by good farm management; however, breeding for larger litter sizes may also affect the health

of dams due to the high reproductive performance. Anatomical issues as prerequisites for large litter sizes are discussed in the following sections.

Uterus length in cross-bred gilts was 110–240 cm in 3 days pregnant gilts (Wu et al., 1989). In an experimental approach, the uterine space per *corpus luteum* was either restricted to 5 cm or non-restricted with physiological 40–50 cm per *corpus luteum* dependent on the stage of pregnancy (Wu et al., 1989). While embryos with non-restricted space survived to 89% at day 50 of pregnancy, embryos with restricted space survived to 8% only. Furthermore, surviving foetuses under restricted space conditions expressed a shorter crown to rump length and lower weight (Wu et al., 1989). Adequate uterus space is an essential prerequisite for the survival, growth and development of piglets; thus, any intrauterine crowding of embryos will cause higher losses of embryos, foetuses and piglets. Wu et al. (1989) concluded that "fetuses require at least 36 cm initial length of uterus to implant, survive and develop fully". Hyperprolific sows such as the DanBred sows should then have extended their uterus size, in accordance to the increase of litter size from 11.8 to 19.6 piglets, from 2.12 m to 3.53 m length of each horn to provide 36 cm of space for each embryo at the beginning of pregnancy. From other studies about the meaning of uterine capacity, it was concluded that, when the number of embryos exceeded 14, intrauterine crowding was set due to maternal limitations (Foxcroft et al., 2006). As a consequence of higher foetus numbers per uterus, more piglets suffer from low birth weight and runting. This morphology-based uterine capacity (=number of conceptuses that the pig uterus can successfully carry to term) is suggested to be the major limitation to litter size in pig and is a maternal limitation (Ford et al., 2002).

In the post-implantation period from day 30–40 of gestation on, nutrition of the pig foetus relies mainly on placental diffusion of nutrients and oxygen driven by the concentration gradient from maternal to foetal blood; therefore, an adequate surface area in the uterus is needed providing functional contact (by placenta) to get the optimal supply (Ford et al., 2002). Breeding larger sows with longer uterus horns and more efficient placentae was discussed to be the solution (Ford et al., 2002).

Besides uterus horn length as a maternal limitation, an adequate uterus blood supply for each conceptus at each age is also crucial for a proper development and survival of the foetus. The uterus horns are mainly supplied with blood by the *arteria uterina,* which branches from the *aorta abdominalis* and runs along the uterus horn from the cervix up to the horn tip at each uterus horn and delivers branches to the uterus wall and placental areas. The small *ramen uterinus* of the *arteria ovarica* provides some blood supply running from the horn tip alongside the uterus horn and anastomises with the final part of the *arteria uterina* at each uterus horn. Although the blow flow/horn increases with increasing numbers of foetuses, the blood flow per foetus decreased with increasing litter size per uterus horn (Prunier et al., 2010). Foetal nourishment is mainly based on diffusion of nutrients and oxygen (Prunier et al., 2010). Thus, any reduction in blood flow will reduce the supply of resources to the foetuses. Furthermore, due to the anatomical structure of uterine vascularisation, the foetuses closer to the uterus horn tip will get even much less nutrients and oxygen, because foetuses at the beginning of the uterus horn do have a stronger diffusion driving force created by the larger gradient of oxygen and nutrients between maternal and foetal blood. Thus, the foetuses closer to the horn tip will get blood with less nutrients and oxygen; the diffusion driving force is weaker. Consequently, these piglets will be lighter the larger the litter is, and variation in litter weight will increase; a higher mortality risk for foetuses and born piglets is established. Breeding larger sows with bigger uteri will not solve this anatomical maternal issue of disproportional vascularisation.

The high reproductive performance could have negative consequences for the dam and the piglets. The amount of animal protein, which has to be synthesised by the dam, is huge. In the first pregnancy, up to 45 kg of BW was newly synthesised for mammary gland development, uterus development, and development of foetuses including placentae and fluids (Prunier et al., 2010). Any piglet at risk to die early is an unnecessary burden for the dam. This burden provokes a higher risk for the dam to develop diseases due to this exhaustive reproductive performance associated with large litter sizes. Furthermore, dams produce more milk with larger litters, however, very often the feed intake is not balanced the higher production, and the sow is developing a nutritional deficiency (Prunier et al., 2010). Most likely, the voluntary feed intake is limited due to anatomical and functional features of the gastrointestinal tract and cannot match the nutritional requirements. As a consequence, BW loss during lactation (up to >20% of body mass) and subsequent reproductive disturbances are common problems in many sows (Thaker and Bilkei, 2005, Tokach et al., 2019).

To summarise, increasing litter size to improve pig meat production creates a disproportionality between genetically fixed structural and functional supply features of sows and the need for nourishment of a high number of foetuses prenatally and postnatally. Further breeding approaches for higher litter size will strengthen this disproportionality.

What are the consequences of this high litter weight variation?

In a cohort of piglets (8 677 Danbred piglets), about 10–15% were born with mild and about 15–20% were born with severe IUGR conditions in herds with high litter weight variation (Bahnsen et al., 2021). These IUGR (runt) piglets are at high risk to suffer from diseases and are unable to reach their genetical potential for growth. Their postnatal performance is prenatally programmed (Foxcroft et al., 2006). The theory of intrauterine metabolic programming or imprinting was established by David Barker as the "Developmental Origins Hypothesis" for human IUGR babies (Barker, 2007). He stated that "undernutrition *in utero* permanently changes the bodys structure, function and metabolism" which leads to a higher risk to suffer from diseases in later life.

In piglets, early imprinting of metabolic features will be especially observed later in their productive life during fattening, because myogenesis (=number of fibres) and differentiation of muscle fibres already start at day 35 and day 55 of intrauterine life, respectively (Foxcroft et al., 2006). IUGR piglets expressed a delayed skeletal myogenesis and muscle development affecting fibre numbers, size and composition, important features for postnatal growth rate, and also metabolic health (Felicioni et al., 2020). Subsequently, in their postnatal life, IUGR piglets had lower fibre numbers, less satellite cells and decreased insulin-like growth factor 1 concentrations in plasma leading to losses in meat quantity and quality (Oksbjerg et al., 2013). Furthermore, IUGR muscles consisted of more connective tissue compared to muscles of normal−weight piglets (Alvarenga et al., 2012) indicating a lower quality of the meat. Thus, their genetically selected growth potential could not be reached postnatally; piglets with low birth weight and IUGR piglets are per se an economic loss.

Any attempt to improve muscle growth postnatally be nutritional approaches failed so far, low weight piglets grew at a lower weight level than the normal weight litter mates. The BW in low−-weight piglets remained lower until day 150; however, the average daily gain increased over time and was equal to normal−weight piglets within days 107–150 of life (Alvarenga et al., 2012). However, the carcass yield and amount of meat in carcass were lower at slaughter in IUGR pigs (Alvarenga et al., 2012), because total lean body mass is programmed prenatally with life-long consequences

and cannot be compensated later in life (Foxcroft et al., 2006; Brown, 2014).

Beside the disturbed skeletal muscle development, the IUGR piglets expressed a lower brain-to–liver ratio with maintained brain weight compared to normal–weight piglets; however, the liver weight was reduced to about 50% of the weight of livers of normal–weight piglets while brain weight was only marginally reduced (brain-sparing within asymmetric growth in IUGR) (Bauer et al., 2003). Furthermore, the gut structure and function were significantly affected in IUGR piglets with a reduced absorptive surface area of the mucosa, lower gut motility and decreased activities of digestive enzymes of pancreas and brush border membranes (Ferenc et al., 2014). Furthermore, the microbial population was changed in comparison to normal–weight piglets, showing less Bacteroidetes and Firmicutes species, but higher amounts of proteobacteria, which were associated with inflammation in the gut (Zhang et al., 2019). These disturbances in structure and function could lead to impaired absorption, inflammation, impaired intestinal barrier function and impaired gut mucosa rebuilding (Ferenc et al., 2014).

All anatomical and physiological prerequisites for a good fattening performance, a well-functioning gut, a highly productive liver and well-developed skeletal muscles, are lost in low weight and IUGR piglets. It should be fundamentally questioned, if breeding for high prolificacy in sows is the right way to improve pig meat production. These sows with their structural and functional limitations (mainly in the uterus anatomy and physiology, but also in their metabolic capacity) and their offspring suffer from many risks for diseases and low–performance capacity; animal welfare is strongly affected in both, sows and offspring.

Disproportionality in dairy cows and their offspring

Modern dairy cows were genetically selected for milk production worldwide with differences in total merit indices. Among the breeds used for milk production, the Holstein Frisian breed is the major breed worldwide, strongly shaped for high milk production by genetics (VanRaden et al., 2021). Focusing on breeding goals such as reproduction and milk production, this disproportionality affected the systemic metabolism of a dairy cow, increasing the risk to develop disturbances such as a systemic low-grade inflammation, oxidative stress and mitochondrial dysfunction, and consequently, subclinical and clinical pathologies (Bradford et al., 2015). However, not only the dairy cow, but also its offspring can be affected by the dam's metabolic condition, and by early nutritional management in life due to metabolic imprinting (Vickers et al., 2000). Recruiting these calves as future dairy cows or fattening bulls potentially resulted in less resilient animals with a higher risk to suffer from pathologies.

Breeding approaches and total merit indices for dairy cows are different worldwide. Breeding approaches for resilience in dairy cows are performed based on mathematical modelling to find the best breeding markers or indicator traits (e.g. Bengtsson et al., 2022). The validity of genomic markers is often proven by performing genotype-phenotype correlations, thereby confirming the breeding success. In Europe, the total merit index is used to select dairy cows. Besides milk yield (36%), also health, exterior, longevity, calf health and several features are considered in the total merit index of the dairy cow breeding approach (https://www.rind-schwein.de/brs-cattle/holstein-breeding-value-estimation-en). In USA, the net merit as a measure of lifetime profit (**NM$**, measure of economically important traits) and the total performance index is used to select dairy cows. Milk production is considered in NM$ with 49% and in total performance index with 40% (https://www.cogentuk.com/news/breeding-strategy-selecting-the-right-index). Thus, both indices place emphasis on overall milk performance. The last update of NM$ index in 2021 included new traits like feed saved (available only for Holstein), heifer livability and early first calving to promote the selection of cows with high feed efficiency and early reproduction (VanRaden et al., 2021). Both, the European and American index system for breeding Holstein dairy cows is a major factor for selecting metabolic imbalances, and due to that disproportionality, they suffer from a high risk for developing pathologies. Furthermore, during focused selection for milk performance and also inbreeding procedures especially in Holstein cows, several congenital dysfunctions (e.g. Bovine leukocyte adhesion deficiency (Nagahata, 2004), Apoptosis peptide activating factor 1 (Ghanem et al., 2017; Deficiency of uridine monophosphate synthase (Gozdek et al., 2020) and malformations (e.g. Vertebral and spinal dysplasia (Kromik et al., 2015)) rose within certain Holstein populations worldwide, further deteriorating health conditions.

Two additional aspects should be critically considered in modern breeding approaches. First, phenotypic markers reflecting health and reproductive performance (mastitis, dermatitis digitalis, claw ulcers, digital phlegmon, white line disease, laminitis, interdigital hyperplasia, ovary cycle disturbances, endometritis, retained placenta, displaced abomasum, milk fever, ketosis), which are considered for assessment of breeding values, are reflecting only end point conditions. This means, a disease is already manifested. Provoked by high performance, however, long before clinical symptoms occur, tissue malfunction, oxidative stress and mitochondrial dysfunction continuously drive a chronic low–grade pro-inflammatory state in the dairy cow (Bradford et al., 2015, Bradford and Swartz, 2020), which has also to be considered as relevant for animal welfare. Thus, these end point markers will most likely not help to improve health and animal welfare substantially. It could be hypothesised that many dairy cows leave productive systems before clinical symptoms of their metabolic disturbances occur, because low–grade inflammation leads to tissue malfunction, decreased milk performance and reproductive failure.

Second, to assess the manifestation of a target genotype in the respective phenotype by correlation is questionable, because correlations never confirm causality. The genotype and thereby, the resulting phenotype of an animal is intrinsically tied to its environment, feeding and management. Thus, to confirm breeding success by checking the phenotypes is an invalid process, because the phenotype is never based on its genotype only. As an example, the improvement of milk somatic cell counts and the lowering of mastitis incidence could partially be based on breeding success; however, since milking hygiene is predominantly influencing the incidence of mastitis and cell counts (Ruegg, 2017), any improvement cannot be based on breeding success only. World-wide, dairy farm systems changed having larger herds of genetically selected high-performance cows. Therefore, the management ability of farmers and the training and experience of care takers (often non-family workers) might not always be optimal leading to decreased phenotypic health, and thereby welfare, which was not intended by genetic selection (Barkema et al., 2015).

In general, environmental factors such as management, rearing regimen, food quality, heat, infections and stress are known to challenge the individual phenotype sustainably: For evolution, "the phenotype in interaction with the environment directs the evolution of the genome it derives from"; this means, phenotype and environment have an effect on genome variations (Auboeuf, 2021). The often observed huge inter-individual variation even within inbred cohorts of farm animals is representing the phenotypic variation of a certain genotype, but is also based on environmentally provoked genome variations (Auboeuf, 2021).

And, maybe highly important, heritable, epigenetic modifications of genomes especially provoked by nutritional conditions could overrun genotype-based phenotypic features in a life-long manner. This "memory of the cell" can increase the variation of phenotypes significantly (Chavatte-Palmer et al., 2018). One example is already addressed in this review in terms of the intrauterine growth retardation in piglets (IUGR) due to insufficient nutrient and oxygen supply via the placenta. Another example of the influence of early nutrition on the development and transfer of target genotypes into respective phenotypes will be discussed in the following.

What is metabolic inflammation in dairy cows and fattening bulls and where does it come from?

Genetic selection for high performance for high milk yield or muscle growth created a strong structural and functional disproportionality between organs and tissues contributing to performance and the rest of the body. Shortly before and after parturition, Holstein Frisian dairy cows lose up to 100 kg of body mass within 6 weeks (Huber et al. 2024, unpublished data). It is unclear so far, how these cows manage this catabolic condition. This extreme body mass loss is based on lipid mobilisation but also on body protein mobilisation to maintain metabolic homeostasis (Sadri et al., 2023). The catabolic stress is reflected by high non-esterified fatty acid concentrations in plasma, mostly consisting of saturated fatty acids. Lipopolysaccharide receptors (Toll-like receptor 4) of nearly all body cells can be activated by those fatty acids (Mamedova et al., 2013), resulting in chronic low−grade inflammation. Furthermore, inflammatory signals from adipose tissues and from the gastrointestinal tract are discussed to participate in development of the pro-inflammatory status (Bradford et al., 2015, Fiore et al., 2020, Owens et al., 1998, Gozho et al., 2006). Supporting this, there is scientific evidence in fattening Holstein bulls that this systemic metabolic inflammation, once established, influences the ceramide metabolism (Kenez et al., 2022). Intermediates of this pathway negatively affect insulin sensitivity by insulin receptor dysregulation and de-phosphorylation of protein kinase B, an important hub within the insulin signalling cascade in bulls (Kenez et al., 2022), confirming findings in humans (Petersen and Shulman, 2017). Furthermore, insulin insensitivity is associated with mitochondrial dysfunction and oxidative stress worsening the pro-inflammatory status (Yaribeygi et al., 2019, Prasun, 2020). Therefore, although inflammation is physiological after parturition for repair and healing of e.g. the reproductive tract, the prolonged inflammatory period provoked by catabolism may overrun the capacity of the immune system to maintain metabolic health in the long-term in a coẃs productive life span. A disproportionality between milk performance pathways and immune function pathways is established. This steadily increasing risk to suffer from the consequences of this systemic metabolic inflammation is a serious welfare issue of the dairy cow.

As mentioned before, also Holstein fattening bulls suffered from metabolic inflammation when fed a starch- and protein-rich diet (Kenez et al., 2022). Intensive feeding approaches (up to 90% of metabolisable energy in American feed lot diets (Jensen et al., 1981)) aimed to promote high average daily weight gain (up to 1.4 kg/day) in fattening bulls. Low fibre or absence of fibre in these high-energy diets were associated with an increased prevalence of subacute and acute rumen acidosis (up to 65%) as assessed in a Portuguese study examining 218 rumens out of 1 960 bullocks at the slaughter house for macroscopically detectable acidotic lesions in the epithelium (Vieira et al., 2022). Parakeratosis, papillary atrophy, star-shaped scars and perforations were detected indicating strong epithelial damage (leaky gut phenomenon); ruminal and bacterial proinflammatory factors could cross the barrier into the blood. Thus, feeding approaches in intensively fed fattening bulls were not matching the digestive capacity of the gastrointestinal tract, especially the rumen capacity. The huge load with soluble energy substrates is causing a detrimental condition for the animal, contributing also to the development of metabolic inflammation (Kenez et al., 2022). Besides rumen acidosis, rapidly growing fattening bulls were at higher risk to develop growth plate lesions especially at long bones, mainly due to osteochondrosis. Hypothetically, this pathology might be also driven by leaky gut and proinflammation. Osteochondrosis is a long-known multifactorial pathology of the metaphysis of bones in rapidly growing fattening animals, based on lack of vascularisation, lack of differentiation of chondrocytes to osteoblasts and lack of mineralisation within the growth plate (Jensen et al., 1981). In an Italian study, 62 bulls of different breeds were examined for growth plate lesions. 35.5% of the bulls showed signs of osteochondrosis, with or without lameness (Levi et al., 2017), while in an older study, 8.5% of bulls expressed osteochondrosis in joints (Jensen et al.,1981).

Rapid growth of fattening bulls promoted by genetics, but also by intensive, starch- and protein-based feeding, is disproportional in terms of bone maturation; bones remain immature and not fully developed even at adult age. Beside rapid growth, the amount of muscle protein was also enhanced by genetic interventions. Modifications of the myostatin gene were used to produce double-muscled breeds such as Belgian Blue and Piemontese cattle. While the latter is additionally selected for ease of calving (<10% caesarean sections), pure Blue Belgian cows undergo caesarean section routinely due to the high body mass of the calf (Bittante et al., 2018). The pelvis anatomy of the cow is disproportional in regards to the calf́s body mass, any spontaneous parturition will set the coẃs life at danger. Thus, driving disproportionality by intensive feeding and by genetic interventions for more muscle is detrimental for the health and welfare also in fattening bulls.

How can early life experiences imprint later health and welfare?

Early life experiences of mammalian offspring are known to increase the risk to suffer from metabolic disturbances and to develop pathologies (Barker, 2007). Either prenatal or early postnatal challenges such as undernutrition, malnutrition or heat stress can imprint anatomical and functional features leading to disturbances of health, less welfare and lower production in later life (Fowden et al., 2006). Early age of first calving (**AFC**) is a declared aim in management of Holstein dairy cows because, besides the culling rate, AFC is one of the most important factors for heifer rearing costs (Tozer and Heinrichs, 2001). In a large Holstein heifer study, it was suggested that the optimal AFC is at the age of 23–26 months (Atashi et al., 2021). Other studies confirm 23–24.5 month as optimal and economically valuable AFC (Ettema and Santos, 2004). However, within the last years, AFC was further reduced down to 22–23 months and even lower (Heinrichs et al., 2017). Although with higher AFC than 23–26 months, 305-d milk performance, milk fat and protein increased in these young cows, the shorter lactation persistency and the higher incidence of dystocia in these cows were used as arguments against higher AFC (Atashi et al., 2021). Since the question about the optimal AFC is still ongoing, a large study in Holstein Frisian dairy cows was performed to identify the best maturation rate (=BW at first calving in percent of mature BW) for first calving at about 24 months. The main factor which was used to assess this best maturation rate was milk yield. Young Holstein cows reaching 73–77% of their final BW were assessed to be consistently able to produce large amounts of milk throughout their productive life span (Han et al., 2021). However, the survival rate (=cows which are surviving to 24 months after first calving at about 24 months) in these young dairy cows was only about 65%, these cows had a productive life

span of about 2.7 lactations (Han et al., 2021). High losses of up to 35% within the first 24 months after first calving and the short productive life span of the surviving cows strongly indicate that immaturity of the dam is bearing a high risk for disturbed health and welfare. This risk is not only affecting the young cow but also could affect the development of the calf, at least during the first pregnancy. Competing for resources, the young rapidly growing and developing dam has to share nutrients and energy with the growing and developing foetus. Lower resource supply to the foetus affects the metabolic development of the foetus (metabolic imprinting or programming) and could have life-long consequences (Barker, 2007, Fowden et al., 2006).

The welfare of calves was recently addressed by the European Food Safety Authority (**EFSA**) Panel on Animal Health and Animal Welfare (EFSA panel, 2023). The panel identified several crucial aspects which might affect calf welfare (dairy calves, veal calves) related to husbandry systems (space, group housing, cow-calf contact) and feeding (colostrum, milk, iron, fibre). It was recommended, that besides an adequate colostrum intake, calves should get increased amounts of milk. It was assessed that in some dairy farms with individual housing, calves experience prolonged hunger periods, mostly by low number of milk meals and by provision of restricted amounts of milk per day. Feeding recommendations suggest milk feeding until at least 4 weeks with subsequent gradual weaning, fresh water and high-quality roughage should be provided *ad libitum*. Fibre intake was directly influencing the development of rumination capacity (EFSA panel, 2023). However, the duration of milk feeding, especially in female Holstein dairy calves, was not addressed as potential crucial aspect influencing calf welfare.

To summarise, to major factors could imprint the later health and welfare of calves, immaturity of their mothers and too short adequate milk feeding periods during the rearing process of the calves. As a working hypothesis, calves need 14–16 weeks to reach a mature ruminant status (Huber, 1969). Thus, any earlier weaning disrupts the developmental process, and immature young mammalians are pushed to survive despite inadequate nutrition. Immaturity in dams and calves – as a problem for animal health and welfare – is induced by management-based processes (early AFC, early weaning) and is mainly driven by economic reasons. These management decisions create disproportionalities with metabolic consequences, which are not well-known so far. However, especially female dairy calves, which are the high–performing dairy cows of the future, could suffer from a very high risk for metabolic disturbances, metabolic inflammation and production diseases. These disproportionalities could be avoided by respecting the physiological needs of a developing young mammal.

To create scientific evidence for the importance of maturity of dam and calf, a study was performed on 59 female Holstein calves (Schwarzkopf et al., 2019, 2022). One half was weaned at week 7 after 2 weeks of stepwise reduction of the milk replacer supply; the second group was weaned in week 17 following the same weaning regimen. About 50% of the calves were born by heifer dams in the early and late weaned groups. All calves had access to roughage and fresh water, and a calf starter was supplied in both groups. At 150 days of age, early weaned calves were lighter; body length and height were shorter. Leptin concentrations in plasma were lower at birth and remained low throughout the whole experimental time in early–weaned calves; especially in early–weaned calves born by heifer dams, leptin concentration remained on the low concentration measured already at birth. In late–weaned calves born by heifer dams, leptin concentrations physiologically increased until weaning suggesting that adequate milk supply for 17 weeks can compensate for intra-uterine imprinted conditions (Schwarzkopf et al., 2019). Leptin is a key factor for the development of the adult metabolic profile, for a proper hypothalamic development and for establishing an adequate metabolic control in terms of energy homeostasis (Granado et al., 2012). It is a well-known indicator of intra-uterine metabolic imprinting in offspring of undernourished pregnant rat dams (Vickers et al., 2000) and also of undernourished women (Granado et al., 2012). Thus, the prenatal plastic window is an important period of developmental time to disturb metabolic conditions in later life, most likely also in female dairy calves. Since these imprinted changes in metabolic conditions are known to be transferred into the next generation (Desai et al., 2015), the recruitment and above-mentioned management of female calves born by heifer dams as future dairy cows result in a transgenerational manifestation of most likely detrimental metabolic features.

Not only the prenatal but also the early postnatal time is a plastic window for metabolic imprinting. Rumen development was promoted to occur earlier in early–weaned calves; however, they expressed a systemic acid load (Schwarzkopf et al., 2022). Furthermore, in all early weaned calves, metabolic stability was strongly disturbed with a significant drop in blood glucose and insulin after weaning; recovery to physiological glucose concentrations took about 42 days (Schwarzkopf et al., 2019). As a conclusion, although the rumen function was somehow developed after early weaning, the systemic metabolism was highly disturbed, e.g. the capacity to maintain blood glucose concentrations by gluconeogenesis was not sufficiently established. Again, a management-based decision created disproportionalities between organs and tissues in the growing calf leading to a higher risk to suffer acutely from metabolic disturbances. A subsequent examination of the early– and late–weaned calves at their first calving revealed that former early–weaned calves expressed higher incidences of subclinical ketosis as primiparous cows than late–weaned (Dr. Jana Frahm, FLI, personal communication). Thus, metabolic imprinting occurred also in the early postnatal period by inadequate nutrient supply.

Conclusions, (potential) solutions and consequences

Thus, the conclusion of this review is that many farm animals selected for high animal protein output are already beyond their physiological limitations in terms of structure and functions of body organs and tissues. These disproportionalities are promoted by breeding for high performance, but also by management-based decisions. The latter could be corrected by e.g. changing rearing processes in all farm animals supporting the physiological timely needs and nutritional demands. However, it is unclear, to what extent these changes in management could ameliorate animal health and welfare in commonly used high-performing breeds. Most likely, it needs to be done over several generations to get rid of epigenetically transferred features. It is very unlikely, that further breeding approaches selective for performance will redevelop disproportionalities. New approaches of sustainable breeding for more resilient animals need to be found, additional phenotypic markers need to be defined. A discussion about feeding, management and farm settings needs to be included, since it is necessary to breed a variation of good-performing animals adaptable to different quality standards of animal production systems. Breeds are needed which are not expressing disproportionality; feed intake should match the needs for performance, and the homeorhetic adaptation to performance should not overburden tissues and organs. This will reduce the amount of animal protein produced by these animals. However, animal losses during the production process will be reduced, too, most likely balancing the reduction in individual animal performance. Concomitantly, to ensure the income of the farmers, this protein must be paid in a way, that the true costs of milk, meat and eggs are covered, and a financial surplus for farmers‘ life is ensured. Matching the

production of animal protein to amounts, which are doable for the animal, will increase animal welfare significantly. Furthermore, the reduction of animal protein production may ameliorate environmental pollution, since the physiology of farm animals includes recycling mechanisms, e.g. for nitrogen and phosphate. Animals, which do not perform at maximum, can be fed restricted in certain nutrients (e.g. P, N in ruminants) and mainly with food, which are non-eatable for humans. For sure, animal protein will remain an indispensable nutrient in human nutrition in the future, especially for children, elderly and diseased persons, due to its proven strong anabolic properties for body protein in comparison to plant proteins, which are mainly used in oxidative energy production (Berrazaga et al., 2019, Ruxton and Gordon, 2024). To match the total protein needs of humans, animal protein can be most likely partly replaced by plant protein (Kozicka et al., 2023). The best mixture of animal and plant protein in diets needs to be assessed, and requirements for protein and amino acids need to be defined for humans along their life span. Research in the nutritional sciences is necessary to evaluate the real needs of animal protein in human nutrition. Concomitantly, animal welfare will be established and maintained. Animal welfare from an animal-centered point must be addressed as an ethical step to establish limits to the strength placed on the animal's anatomical and physiological functionality. It may allow more sustainable and efficient farm animal production and the availability of healthy animal-derived protein for human nutrition worldwide.

Finally, to implement the knowledge about disproportionality in farm animals, about related animal welfare issues and about potential solutions into a broader context, the world́s protein requirement for a healthy human nutrition needs to be addressed. According to the World Health Organisation recommendations (WHO-TRS, 2007), an adult human needs 0.66 g protein/kg BW/-day. That means, a 70 kg person requires 46.2 g protein /day. Children, pregnant women, elderly, athletes and diseased humans need more in accordance to their age, to their physiological status and to their performance, muscle exercise and immune functions, respectively. Worldwide, 355.46 million tonnes of meat, 930.00 million tonnes of milk and 93.00 million tonnes of eggs are produced in 2023 (Ritchie et al., 2019 (last update 2023)). However, production areas are not equally distributed throughout the continents of the world; thus, many people of the world are suffering from hunger, malnutrition and food insecurity.

Just as an intellectual game, considering these produced amounts of animal protein, the amount available per capita was calculated, assuming the world́s population in 2023 is 8,1 billion humans on earth (de.statista.com). Currently, each human being could have available 3.4 kg of meat (26 g protein/100 g), 10 kg of milk (3.4 g protein/100 g) and 1 kg of eggs (13 g protein/100 g) per month. In sum, each human being could have about 1 354 g animal protein available for consumption per month (30 days), or about 45.1 g animal protein/day. This nearly matches the need of 46.2 g protein/day of a 70 kg human according to the World Health Organisation.

This led to the following summarising suggestions: a) there is no need to intensify animal protein production, but optimise rearing conditions for young farm animals to get more resilient animals, and optimise performance to avoid disproportionality and correlated losses of animals during the production period; b) worldwide animal protein availability needs to be improved by global trading, that the required animal protein intake is ensured for all, and by improving animal protein production in native settings of countries, e.g. by breeding approaches; c) human healthy diets worldwide consist of adequate amounts proteins from plant and animal sources to increase human health and wellbeing, thereby decreasing the overall requirement of animal protein. As an example for a healthy diet, the planetary health diet could be a valuable suggestion (https://eatforum.org/eat-lancet-commission/the-planetary-health-diet-and-you/). d) human-edible plant material is more used for human nutrition instead of for intensive animal feeding. The impact of all these suggestions on animal protein production efficiency, on environmental pollution and on land use for plant as feed and food in future cannot be assessed within this review article. However, the structural and functional disproportionality of farm animals has a strong impact on the efficiency of animal protein production and on animal welfare.

Ethics approval

Not applicable.

Data and model availability statement

None of the data were deposited in an official repository. No new data sets were created.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use any AI and AI-assisted technologies.

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Declaration of interest

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