A SYSTEMATIC REVIEW AND META-ANALYSES OF RISK FACTORS ASSOCIATED WITH LAMENESS IN DAIRY COWS

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Meinen Eltern.

Zum Dank und zur Freude.

„Nil sine magno vita labore dedit mortalibus."

(Quintus Horatius Flaccus, *Sermones* I, 9)

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ABBREVIATIONS

AMSTAR	A measurement tool to assess the methodological quality of systematic reviews
BCS	Body condition score
CI	Confidence interval
DIM	Days in milk
OR	Odds ratio
PICO	Participants/population, intervention, comparisons, outcome
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
ROBIS	A tool to assess risk of bias in systematic reviews
SLS	Stall lameness score
STROBE	Strengthening the reporting of observational studies in epidemiology

I. INTRODUCTION

Lameness in dairy cows is one of the principal economic and animal welfare issues in modern intensive dairy production all over the world (KOSSAIBATI & ESSLEMONT, 1997; WHITAKER et al., 2000; MANSKE, 2002).

STANEK (1997) has described the condition as an inability to express a normal and functional gait pattern in one or more limbs usually as a consequence of pain. Animals experience severe discomfort and attempt to exclude one or more limbs from weight bearing and perform compensatory movements of the head. This effort to alleviate pain appears as an aberration in the physiological locomotion pattern (GREENOUGH, 1985; RADOSTITS et al., 2007; BLACKIE et al., 2013). Multiple approaches have been established over the years to identify lame animals and quantify lameness within a herd based on different characteristics of locomotion (SPRECHER et al., 1997; FLOWER & WEARY, 2006; BRENNINKMEYER, 2007; THOMAS et al., 2015).

A wealth of research has indicated that lameness in dairy cows has a pronounced adverse effect on milk production (GREEN et al., 2002; ONYIRO et al., 2008; ARCHER et al., 2010; KING et al., 2006), reproductive performance (MELENDEZ et al., 2003; GARBARINO et al., 2004; BICALHO et al., 2007; ALAWNEH et al., 2011), longevity (BOOTH et al., 2004; BRUIJNIS et al., 2012), and general well-being (WHAY et al., 2003). Furthermore, it is a painful condition (WHAY et al., 1998; JUAREZ et al., 2003) that impairs the natural behaviour of affected animals (ITO et al., 2010; WESTIN et al., 2016a), and causes considerable economic losses (KOSSAIBATI & ESSLEMONT, 1997, DOLECHECK & BEWLEY, 2018).

In North America, lameness prevalences of 26.2 % (KING et al., 2016) have been reported. European studies have observed 31.8 % (GRIFFITHS et al., 2018) and 17.8 % (SCHRANNER et al., 2015) in the United Kingdom and Northern Germany, respectively. It is well understood that lameness in dairy cows is a production disease of multifactorial nature (WELLS et al., 1993a; GALINDO et al., 2000; ADAMS et al., 2017). The prevalence of lameness is commonly higher in free stall housings than in tie stall facilities or other housing types (CHAPINAL et al., 2013; FODITSCH et al., 2016; COSTA et al., 2018). Other farm level-related risk factors include herd size (CHAPINAL et al., 2013; RICHERT et al., 2013; CHAPINAL et

al., 2014), flooring type (ROUHA-MÜLLEDER et al., 2009; CHAPINAL et al., 2011), lying comfort and stall design, and width of alleys within the housing pen (ESPEJO & ENDRES, 2007; ITO et al., 2010; WESTIN et al., 2016b). On cow level, previous studies have associated parity (OIKONOMOU et al., 2013; RANDALL et al., 2015; SOLANO et al., 2015), milk yield (CHAPINAL et al., 2014; RANJBAR et al., 2016), stage of lactation (WARNICK et al., 2001; FODITSCH et al., 2016), and body condition (BICALHO et al., 2009; NEWSOME et al., 2017a; RANDALL et al., 2018) with the prevalence of lameness. Furthermore, evidence suggests that management practices such as claw trimming routines (FJELDAAS et al., 2006), access to pasture or an outdoor exercise area (HERNANDEZ-MENDO et al., 2007; FABIAN et al., 2014) and aspects of feeding management (AMORY et al., 2006; ONYIRO et al., 2008) influence the prevalence of lameness.

The European Food Safety Authority has presented an insightful report of factors associated with lameness in dairy cows emphasizing that the artificial environment cattle are kept in is of crucial importance in the context of lameness development (CANDIANI et al., 2009; EFSA, 2009). Concomitantly, BELL et al. (2009) have introduced a program based on hazard analysis and critical control point (HACCP) principles to tackle lameness in dairy heifers. However, subsequent investigations on prevalence in North America and in Europe have clearly corroborated that lameness still is an ongoing concern (SOLANO et al., 2015; GRIFFITHS et al., 2018).

In recent years, systematic reviews have become more and more important in medicine (MOHER et al., 2009). They provide the possibility of a precise and organised appraisal and compilation of the state of knowledge in regard to a specific research question (BORENSTEIN et al., 2011; GOPALAKRISHNAN & GANESHKUMAR, 2013). Clear procedures are defined to increase objectivity to the maximum extent possible. An essential feature needed to further address the question of interest is the application of evidence-based criteria for the inclusion of studies and the synthesis of measures of effect sizes in a meta-analysis. This technique is a powerful statistical tool to combine empirical data from related studies, to summarize and present evidence (CHEUNG, 2015) and to create transparent summary estimates (BORENSTEIN et al., 2011; RILEY et al., 2011).

Reviews have been published on lameness in dairy cows, on approaches to detect

lame animals, and the role of the environment on lameness dynamics (HIRST et al., 2002; COOK et al., 2009; DUTTON-REGESTER et al., 2018). The number of systematic reviews is yet short and given the knowledge at the beginning of the present work, neither a systematic review nor a meta-analysis have so far been conducted to evaluate risk factors associated with lameness in dairy cows. Against this background, the objective of the present study was to give a meticulous compilation and statistical evaluation of literature by means of a systematic review and meta-analysis on risk factors for lameness in dairy cows. The intention was to contribute evidence to the current knowledge by giving an intricate exposition of literature as well as by providing a summary estimate of risk factor effects.

II. LITERATURE OVERVIEW

1. Lameness

1.1. Definition of lameness

Lameness is the inability of an animal to express a normal and functional gait pattern in one or more limbs (STANEK, 1997; RADOSTITS et al., 2007). It is mostly a consequence of pain, but may equally be caused by mechanical factors, such as disorders of the locomotor system or a combination of both elements. Pain in one or more limbs entails a reluctance to bear full weight in the affected extremity which is referred to as 'limping' or 'claudication'. Pathokinaesthetic alterations in the quality of movement may be accompanied by decreased activity, impaired capacity to stand, rise, and lie down as well as abnormal posture (GREENOUGH, 1985). Animals make an effort to modify their movements corresponding to the extent of pain they experience in order to avoid or minimise discomfort (GREENOUGH, 1985; BLACKIE et al., 2013). An arched back, weight shift towards the sound limbs, and compensatory movements of the head and of the unaffected extremities in order to transfer the centre of gravity away from the painful limb are seen as a result of a considerably painful process (GREENOUGH, 1985; BLOWEY & WEAVER, 2011). In severe cases, the affected limb may be spared and not used for weight-bearing.

Lameness can be categorised into supporting limb lameness and swinging limb lameness depending on whether pain arises during weight-bearing or movement of the limb (GREENOUGH, 1985). Whereas the latter typically indicates pathological conditions in the proximal part of the extremity and therefore appears as an aberration of the physiological joint flexion and swing phase of the limb, supporting limb lameness is mainly characterised by a short stance phase. In most cases, this can be attributed to causal disorders in the claw region. In addition to aberrations of stride and lameness induced by pain, GREENOUGH (1985) has differentiated between 'specific' lameness, referring to pathognomonic changes of gait in compliance with an underlying pathology, and 'characteristic stance' which may possibly indicate the origin of lameness and facilitate diagnosis.

Literature has produced further ways to define and classify lameness. Whereas some studies have conformed with the exposition introduced above (GREEN et al., 2014; MORABITO et al., 2017), others have described lameness as the occurrence of pathological findings of the claw (POTZSCH et al., 2003; GREEN et al., 2010) or the fulfilment of a numerical rating score (CHAPINAL et al., 2013). Certain research has not introduced an accurate specification of lameness (FAYE & LESCOURRET, 1989).

1.2. Lameness in dairy cows

1.2.1. Implications for animal welfare

Animal welfare is commonly regarded as the absence of suffering from health issues and physical disorders on the one hand as well as concerns related to affective perceptions such as pain, distress, and well-being (FRASER, 2008; VON KEYSERLINGK et al., 2009). A good state of health is thus essential in regard to good welfare. Lame cows experience pain and are impaired in their physiological mobility. It is furthermore important to note that lame cows behave differently from sound animals and are perturbed in displaying the broad spectrum of natural behaviours (COOK & NORDLUND, 2009). They rather have to modify their comportment in order to mitigate pain and hypersensitisation to physical stimuli (WHAY et al., 1998; WHITAKER et al., 2000; WHAY, 2002; WHAY et al., 2003; WEIGELE et al., 2018).

In general, lame cattle tend to spend a larger amount of time lying in total (ITO et al., 2010; BLACKIE et al., 2011; WESTIN et al., 2016a). This can be traced back to a reluctance to bear weight in order to alleviate pain (WHAY, 2002; JUAREZ et al., 2003; VAN NUFFEL et al., 2013). Furthermore, lame dairy cows are the last ones to be milked as they either behave less dominantly or struggle with keeping up. They may as well prefer the less crowded rear area of the collective yard, where less agonistic behaviour takes place (MAIN et al., 2010). On dairies using automatic milking systems, lame animals attend the milking unit less frequently (BORDERAS et al., 2008).

Feeding behaviour in particular is characterised by dominance dynamics and social

rank with the low ranking animals having inferiority in their access to resources (NEAVE et al., 2018). Lame animals are less able to compete successfully in agonistic interactions. Owing to their lower social rank, these animals have shorter daily feeding times, visit the feed bunk less often, and tend to accelerate their feed consumption (JUAREZ et al., 2003; HOHENBRINK & MEINECKE-TILLMANN, 2012; NORRING et al., 2014; BEER et al., 2016; THORUP et al., 2016; BARKER et al., 2018; WEIGELE et al., 2018). In pastured cows, bite rate and grazing time have been shown to decrease among lame cattle due to pain and (HASSALL et al., 1993) they can consistently lose body weight (ALAWNEH et al., 2012b). HOEDEMAKER et al. (2009) have corroborated this view and elaborated that the state of negative energy balance in the postpartum period may be exacerbated in lame animals. Modifications in feeding and lying behaviour as well as activity and social behaviour may have a negative impact on health state and energy supply which could subsequently render lame cows more prone to further health disorders (WEIGELE et al., 2018).

1.2.2. Economic impact

Ranking third after reproductive failure and mastitis, bovine lameness has been one of the major economic issues in modern intensive dairy production all over the world (ENTING et al., 1997; KOSSAIBATI & ESSLEMONT, 1997; WHITAKER et al., 2000; MANSKE, 2002). It causes substantial financial losses and precipitate culling of animals. According to VON KEYSERLINGK (2008), it is the most prevalent and cost-intensive issue for cows in free stall dairies.

A wealth of evidence has demonstrated that lameness in dairy cows has a pronounced adverse effect on milk production (RAJALA-SCHULTZ et al., 1999; HERNANDEZ et al., 2002; ONYIRO et al., 2008; ARCHER et al., 2010; GREEN et al., 2010; KING et al., 2016). A reduction in milk yield has been reported from 6 weeks up to 4 months prior to treatment (GREEN et al., 2002; AMORY et al., 2008; READER et al., 2011). With an exacerbating locomotion score, lame cows are increasingly unable to meet their potential 305-d milk performance (JUAREZ

et al., 2003; ARCHER et al., 2010b). GREEN et al. (2002) have exposed that an approximate reduction of 350 kg of milk (range 160 – 550 kg) is induced throughout the 305-d lactation. This is in line with a study by WARNICK et al. (2001) describing the major decrease in milk yield due to lameness. Per day, ONYIRO et al. (2008) have identified an average loss of 0.78 kg of milk in lame cows compared with sound animals and a reduction of up to 5.5 kg in severe lameness cases (ONYIRO et al., 2008). BICALHO et al. (2008) pointed out that milk production of lame cows would not have been impinged upon to the extent they had observed, in the event that cows had remained sound. They have drawn to attention that an average of 1.0 kg of daily milk loss per lame cow needs to be taken into consideration.

Moreover, a detrimental influence of lameness on reproductive performance and the fertility of dairy cows has been evident. HASSALL et al. (1993) have suspected impaired fertility secondary to pain and discomfort induced by lameness.

As lame cows spend more time lying down during heat compared with sound herd mates (WALKER et al., 2008), sexual behaviour may be disturbed to the extent that lame animals cannot fully express their oestrus behaviour (WALKER et al., 2010). Oestrus may hence be difficult to detect, especially in the event that lame cattle are separated from the herd (PEELER et al., 1994). PEELER et al. (1994) also assumed that the sexual cycle of lame bovines may come to rest, since they are less capable of competing for feed. Furthermore, elevated levels of blood cortisol, an indicator of pain induced distress (MCMEEKAN et al., 1998; FAULKNER & WEARY, 2000; COETZEE et al., 2008), associated with lameness induced pain and discomfort might interfere with the release of luteinising hormone by the pituitary gland.

WALKER et al. (2010) have explained that a decreased sexual activity during oestrus in lame animals appears to be initiated by a diminution in progesterone triggering during the preceding luteal phase and hence by an insufficient sensitisation to oestradiol rather than by lower levels of serum oestrogens. It has further been alleged that lame cattle may additionally have an alternated pattern of reproductive or stress-related pheromones and consequently be less attractive for interaction and mutual mounting to sound herd mates.

An increase in days from calving to first service in lame animals can be ascribed to a delayed onset of ovarian activity in the period after parturition (MELENDEZ et al., 2003; GARBARINO et al., 2004; KILIC et al., 2007; ARCHER et al., 2010a). Along with a prolonged period from parturition to first service, impaired reproduction includes a greater amount of inseminations and thus a longer time until conception (COLLICK et al., 1989; HERNANDEZ et al., 2001; HERNANDEZ et al., 2005; BRUNO et al., 2009; ALAWNEH et al., 2011). Compared with sound herd mates, lame animals tend to require 12 days more time to conceive again after calving (BICALHO et al., 2007; ALAWNEH et al., 2011). This protracted incapacity to conceive appears to go hand in hand with difficulties in conserving gravidity. Apart from overall decreased fertility, MELENDEZ et al. (2003) have discovered a higher incidence of cystic ovarian disease in lame cattle compared with non-lame cows.

Furthermore, lameness enhances the likelihood of an animal to be removed from the herd, especially when problems are severe, recurrent or chronic (MARTIN et al., 1982; BOOTH et al., 2004; BRUIJNIS et al., 2012; WEIGELE et al., 2018). This is most pronounced from 61 DIM to 129 DIM and can be directly attributed to an enfeebling impact of the condition as well as to reproductive failure and decrease in milk yield.

1.2.3. Lameness prevalences across countries

Commonly, lameness is quantified as the percentage of lame cows within a herd, i.e. the prevalence. Therefore, the locomotion of the animals is usually assessed applying validated scoring systems. Subsequently, from the percentage of animals with certain scores, a lameness prevalence within the herd can be calculated.

In North America, lameness prevalences of 26.2 percent (KING et al., 2016) and 23 percent (COOK, 2003) have been reported. For Brazil, COSTA et al. (2018) have detected an overall lameness prevalence of 42.5 percent. European studies have observed 31 percent in Austria (DIPPEL et al., 2009a), 17.8 percent in Northern Germany (SCHRANNER, 2015), 14.8 percent in Switzerland (BECKER

et al., 2014a), and 31.8 percent in the United Kingdom (GRIFFITHS et al., 2018). In Australia, RANJBAR et al. (2016) have ascertained a mean prevalence of 18.9 percent.

This is emphasised by the fact that producers are generally not aware of the actual extent to which lameness is present on their farms (RICHERT et al., 2013; OLMOS et al., 2018). The number of lame cattle as well as the associated impact on animal welfare is thus underestimated (WELLS et al., 1993a; ESPEJO et al., 2006; BARKER et al., 2010; ALAWNEH et al., 2012a; BRUIJNIS et al., 2012; FABIAN et al., 2014), which reflects both a lacking ability to identify lame cows as well as an insufficiency or intermittence of documentation of lameness cases in their herd (MILL & WARD, 1994; WHAY et al., 2003; BELL et al., 2006; BARKER, 2007). Stockmen may just as well have become used to animals showing abnormal gait patterns or be overstrained with the approach to tackle the problem (RICHERT et al., 2013; OLMOS et al., 2018). The detection and treatment hence are often delayed. Moreover, farm managers might not completely realise the consequential economic impact of lameness (BRUIJNIS et al., 2010; VAN DE GUCHT et al., 2017). MILL and WARD (1994) have uncovered a direct correlation between a farmers ability to detect lameness and the momentary status of lameness occurrence on their operation.

1.3. Approaches to assess locomotion in dairy cattle

A variety of scoring systems has been introduced in the literature to describe features of dairy cow gait and to provide the ability to characterise gait disturbances and aberrations of posture. They furthermore allow for the quantification of lame cows and of cows displaying an alteration of gait pattern. These systems are usually based on the visual assessment of gait, posture and head movements. Locomotion scoring systems incorporate a scale which helps to specify disturbances in locomotive pattern and abnormalities of stance. Two main approaches are available: numerical rating scores and visual analogue scales (FLOWER & WEARY, 2006). Commonly, numerical rating scores apply either a 2-point, 3-point, 4-point, 5-point or 6-point scale. Visual analogue scales have initially been established to measure pain or pain relief in human patients (SCOTT & HUSKISSON, 1976) or to assess

lameness in sheep (WELSH et al., 1993). They implement a continuous scale displayed by a line with descriptive terms for certain characteristics. Both endpoints of the line relate to the extremes of this parameter. The condition of the characteristic which best matches the observed manifestation is marked on the line (SCOTT & HUSKISSON, 1976; WELSH et al., 1993; ENGEL et al., 2003; FLOWER & WEARY, 2006; SCHRANNER, 2015).

Numerical rating scores are the most common approach to locomotion assessment in cattle. Cows are usually regarded as lame when they obtain a certain score. In some cases, scoring systems contain the possibility to further differentiate between lame and severely lame animals. BRENNINKMEYER et al. (2007) have modified the gait scoring system by WINCKLER and WILLEN (2001) and merged the original five categories into two remaining ones to classify a cow as lame or non-lame. Based on the procedures introduced by SPRECHER et al. (1997), AMORY et al. (2006) have presented a locomotion scoring system with a 3-point scale that focuses on the assessment of the cow's back position while standing and walking. Accordingly, cows are categorised as normal (score 1), mildly and moderately lame (score 2), and lame or severely lame (score 3). Further methods that establish a 3-point scale have been developed and implemented in different studies (MANSKE; 2002; MANSKE et al., 2002; ANDREASEN & FORKMAN, 2012; ADAMS et al., 2017). These aim at detecting impaired mobility and gait abnormalities such as shortened stride length, tracking of feet, arched back, and the presence of limping or unwillingness to bear weight on one or more limbs. Similar features have been integrated in 4-point scale scoring methods (COOK, 2003; BRENNINKMEYER et al., 2007; RUTHERFORD et al., 2009; BARKER et al., 2010).

SPRECHER et al. (1997) have presented the most commonly applied 5-point lameness scoring system that uses posture and gait to assess dairy cow locomotion. This method has been abundantly used and modified (WINCKLER & WILLEN, 2001; ESPEJO & ENDRES, 2007; SARJOKARI et al., 2013; SOLANO et al., 2015; COOK et al., 2016). Cows are assessed for the presence of an arched back when standing and walking as well as for stride length and the distribution of weight-bearing. Usually, cows are classified as lame when they obtain a score of 3 or higher. Other 5-point scoring systems are similar and may additionally incorporate gait symmetry, walking speed, head carriage and tracking of feet

(O'CALLAGHAN et al., 2003) (WELLS et al., 1993a; WELLS et al., 1993b; FLOWER & WEARY, 2006). THOMAS et al. (2015) have presented a meticulous 6-point scoring system that enables observers to record information on stride length, weight-bearing, symmetry, walking velocity, and back arch. It has been employed to evaluate dairy cows' recovery from claw horn lesions.

Since cows housed in tie stall facilities tend to be constantly confined, it is not common to record characteristics of their locomotion in accordance with one of the previously exposed scoring systems. In order to assess lameness in these animals, LEACH et al. (2009) have developed a stall lameness scoring system that takes four different behavioural patterns into consideration. Cows are observed from behind for the presence and display of regular and repeated weight-shifting from one limb to the other, placing one or more claws on the edge of a step, 'nursing' one foot, and uneven weight-bearing when being encouraged to move from side to side. If at least two of these indicators are detected, a cow is classified as lame. The stall lameness score has subsequently been implemented, modified and evaluated (GIBBONS et al., 2014; PALACIO et al., 2017). PALACIO et al. (2017) have stated that the SLS is a useful tool to estimate lameness prevalence within a herd. They have yet pointed out that the true prevalence of lame animals may be underestimated compared with locomotion scoring approaches.

2. Factors associated with lameness in dairy cows

Lameness in dairy cattle is a multifactorial condition (LEONARD et al., 1994; GALINDO et al., 2000; ADAMS et al., 2017) that arises when an abundance of factors and elements related to housing, management, and the individual animal interacts. A large body of research has exposed factors associated with lameness in dairy cows. The European Food Safety Authority (EFSA) emphasised that the environment dairy cows are subjected to is of crucial importance in the context of lameness development (EFSA, 2009; CANDIANI et al., 2009).

2.1. Farm level-associated risk factors

2.1.1. Flooring surfaces

In spite of common practise, indoor flooring systems in modern free stall dairies provide cows with unsatisfying conditions for locomotion which appear inferior to those on pasture (ALSAAOD et al., 2017). However, differences exist between currently available flooring surfaces.

Cows clearly favour standing and walking on soft surfaces rather than spending more time than necessary on an uncomfortable walking ground (HAUFE et al., 2009; ENDRES, 2017). Hard, abrasive, and slippery floors can contribute to an increase in lameness prevalence. This is further supported by TELEZHENKO et al. (2007) who have outlined the conclusion that cows prefer softer rubber flooring over concrete. By implication, the quality of flooring is an element to consider in the development of lameness in dairy cows (ROUHA-MÜLLEDER et al., 2009). Rubber floored grounds reduce pressure on the claws and positively influence the well-being of cows (BRUIJNIS et al., 2012). They offer traction and compressibility and thus provide a soft and antiskid surface to walk on (CHAPINAL et al., 2013). Rubber mats furthermore entail evident improvements for locomotion and claw health: cows walk faster and more confidently, take longer strides, slip less often and are more inclined to exhibit natural behaviours such as oestrus and comfort behaviour (BENDEL, 2005; RUSHEN & DE PASSILLÉ, 2006; HAUFE et al., 2009; CHAPINAL et al., 2011; FRANCO-GENDRON et al., 2016). Rubber also diminishes the concussion within the hoof capsule as it absorbs some of the force loaded upon the distal limb during weight-bearing (CHAPINAL et al., 2011). Furthermore, claws of cows housed on rubber floors are similar in their appearance to claws of cows kept on pasture (BENZ, 2002).

Concrete floors are rather practical in modern housing facilities for dairy cows (ENDRES, 2017). However, concrete is more unpleasant to walk on (BERGSTEN, 2001) and cows housed on concrete floors are at higher risk for lameness (VANEGAS et al., 2006) than cows provided with rubber floorings. Grooved concrete in particular may be more harmful compared with plain, solid concrete due to its increased abrasive properties and its irregular surface pattern (PÉREZ-CABAL & ALENDA, 2014). FRANKENA et al. (2009) have detected the most pronounced gait disturbances in cattle subjected to grooved concrete floors. Even

though rough walking surfaces ensure solid frictional qualities, they may lead to excessive and detrimental wear of the claws (BERGSTEN, 2001).

In addition to the type of flooring, SOLANO et al. (2015) have put emphasis on the importance of the frictional properties of the ground. Cows may have to adapt themselves to very slippery floors by modifying their movements. Hence, slipping and coping with very slippery conditions may cause damage to the feet and involve the lateral claws in excessive weight-bearing which can subsequently result in an increased risk of lameness (BLOWEY, 2005; DEMBELE et al., 2006; ENDRES, 2017). When it comes to slipperiness, solid concrete floors have been shown to have an advantage over slatted flooring systems (ROUHA-MÜLLEDER et al., 2009). Cows also are more reluctant to walk on slatted floors compared with solid grounds.

In opposition to the aforementioned, BOYLE et al. (2007) have not noticed major improvements of claw health in cows housed on rubber compared with concrete. This view has further been corroborated by HAUFE et al. (2012).

2.1.2. Housing type

The prevalence of lameness is commonly higher in free stall housings than in tie stall facilities or other housing types (CHAPINAL et al., 2013; FODITSCH et al., 2016; SHEARER & VAN AMSTEL, 2017; COSTA et al., 2018). This difference may be attributed to more time spent on concrete floors or other management practises and factors related to housing. However, the reasons have not yet been clearly determined and information provided by literature is scarce in this context.

2.1.3. Lying comfort

Cow comfort is of essential importance in regard to lameness. Unsatisfactory cow comfort even enhances the impact of nutritional challenges, hormonal disorders, infections, and traumatic triggers of lameness (COOK & NORDLUND, 2009; ENDRES, 2017).

A wealth of evidence has reinforced the pivotal role of stall design and cow comfort in the context of lameness development and prevalence among dairy cows housed

in free stall facilities (COOK, 2002; DIPPEL et al., 2009a; ITO et al., 2010; WESTIN et al., 2016b). Prolonged standing and walking times increase the risk to develop foot lesions (BERGSTEN, 2001; RANDALL et al., 2015). The paramountcy of stall design is further emphasised by the fact that cows ought to spend 12 to 14 hours per day resting (FRIEND et al., 1977; GUARD, 2001). Implications for free stall design are that cows should be offered comfortable stalls in order to be encouraged to lie down quickly and willingly on the one hand and to spend less time with their rear limbs standing outside the stalls on the other hand (WIERENGA & HOPSTER, 1990; ROUHA-MÜLLEDER et al., 2009; ENDRES, 2017). As soon as a considerable percentage of cows rather stands within the free stalls than lie down, some feature of stall design is likely to be unsatisfactory which induces discomfort and interferes with the cow's well-being (FAULL et al., 1996; DIPPEL et al., 2009a).

Adequate dimensions of lying stalls are important to ensure stall usage. When cows rise, they lunge forward with their head in the first place in order to transfer the centre of gravity over the carpal region (COOK et al., 2004; ENDRES, 2017). Thereby, they can obtain sufficient balance to put weight on their rear limbs. For a physiological rising process, it is hence crucial that stalls are long enough for cows to move properly (LEONARD et al., 1994; BLOWEY, 2005; DIPPEL et al., 2009b). Short stalls also hinder cows from lying down the way they intend to. The total stall length has therefore been recommended to measure 3.0 metres including at least 0.6 metres for lunge spaces in front of a cow's head. As for stall width, studies have suggested a width of twice a cow's hip width (WESTIN et al., 2016b), i.e. 1.15 metres to 1.25 metres (HÖRNING, 2003; BLOWEY, 2005). Further obstacles impeding stall usage and promoting the risk of lameness are restrictively positioned neck rails (BERGSTEN, 2001; VON KEYSERLINGK, 2008; BERNARDI et al., 2009; CHAPINAL et al., 2013), brisket boards that are too high or positioned inadequately (BARKER et al., 2007; ESPEJO & ENDRES, 2007), and high rear kerbs (FAULL et al., 1996; BLOWEY, 1998).

As for cow comfort, research has indicated that the type of stall surface and bedding material are key elements in regard to lameness (VON KEYSERLINGK, 2008; ENDRES, 2017). Deep bedding is generally more appealing to cows than rubber mattresses and they have been shown to clearly favour deep-bedded sand or

sawdust stalls over mattresses (COOK, 2002; TUCKER et al., 2003; VON KEYSERLINGK, 2008; ITO et al., 2014). A distinctly reduced risk of lameness has been recorded in cows with access to deep-bedded free stalls compared with cows housed in dairies providing mats or mattresses (DIPPEL et al., 2009a; BARRIENTOS et al., 2013; CHAPINAL et al., 2013; COOK et al., 2016). Lame cows experience pain from their condition, which is why they are in need of a soft surface that improves ease of lying down and rising (ENDRES, 2017).

2.2. Management-associated risk factors

2.2.1. Claw trimming regime

Overgrown claws are associated with lameness (DEMBELE et al., 2006; SOLANO et al., 2015) and claw trimming in regular intervals hence constitutes a crucial point in managing foot health in dairy cows and has a positive preventive effect on the occurrence of digital disorders (FJELDAAS et al., 2006; LAVEN et al., 2008; BRUIJNIS et al., 2010; SCHULZ et al., 2016; GRIFFITHS et al., 2018). Moreover, MAXWELL et al. (2015) have documented an increase of 734 litres in 305-day milk yield in lame animals that had received hoof trimming.

Since the dorsal hoof wall shows higher rates of horn growth compared with the heel, the dorsal angle of the digit decreases gradually (RAVEN, 1989; BLOWEY, 1998). As a consequence, a larger amount of weight is put on the caudal parts of the claw and bruises of the corium and sole ulcers may develop. Cows frequently do not recover entirely from the latter and may remain chronically lame. Not only are biomechanics positively influenced by hoof trimming as weight load is more evenly distributed, but also are hoof growth characteristics improved as horn growth is enhanced and wear diminished (MANSON & LEAVER, 1988b; MANSON & LEAVER, 1989). Furthermore, the heel region, which is confronted with bearing the major part of weight in overgrown claws, is relieved and supported in its natural function of cushioning. BLOWEY (2005) has recommended foot trimming at drying-off and whenever claws are overgrown. Prior to parturition may be promising, since the most favourable biomechanical conditions can thus be created for the subsequent high-risk period in early lactation (MANSON &

LEAVER, 1988b; MANSON & LEAVER, 1989; MANSKE, 2002). GRIFFITHS et al. (2018) have detected an association between foot trimming in early lactation and decreased lameness prevalence.

2.2.2. Feeding

A ration high in easily fermentable carbohydrates or a high amount of concentrate poses a risk for lameness in cattle (VERMUNT, 2000; GUARD, 2001; ONYIRO et al., 2008; RANJBAR et al., 2016). Intensive diets composed in alignment with the nutritive requirements of dairy cows in early lactation are rich in concentrate and quickly fermentable carbohydrates on the one hand and low in slowly digestible fibre on the other hand (BLOWEY, 2005). A suitable amount of fibre within the diet is essential for an adequate duration of mastication and rumination and proper ensalivation of the bolus. This is crucial for ruminant digestion and the maintenance of a healthy and properly working rumen (MAEKAWA et al., 2002a, 2002b; BEAUCHEMIN & YANG, 2005; YANG & BEAUCHEMIN, 2009). Apart from that, rumen pH is directly influenced by elements that have an impact on the assembly of fermentation acids. Reduced roughage intake or in turn high levels of carbohydrates entail a rapid ruminal decomposition of these easily fermentable compounds, an elevation of lactic acid and a lowering of ruminal pH (MANSON & LEAVER, 1989; COLLARD et al., 2000; BEAUCHEMIN & YANG, 2005). As a consequence, endotoxins and histamine can penetrate the ruminal wall and enter the blood stream where they cause vasodilatation and damage to the intricate system of blood vessels within the hoof. Following disturbed microcirculation, horn of poor quality is produced which gives rise to various claw problems such as sole ulcers and diseases of the white line (SHEARER & VAN AMSTEL, 2017). Furthermore, coriosis is associated with a significant amount of pain and discomfort in affected animals.

2.2.3. Herd size and overstocking

Equivocal results have been presented in the currently available literature in regard of the association between lameness and herd size. According to several studies, a

lower prevalence of lameness in larger herds may reflect more professional lameness management procedures, i.e. automated production elements and wider availability of dairy personnel to look detect and treat lame individuals in time (CHAPINAL et al., 2013; CHAPINAL et al., 2014; SOLANO et al., 2015).

RICHERT et al. (2013) have yet not recognised a positive association between larger herd size and lameness prevalence. ALBAN (1995) hypothesised that producers may spend less time observing their animals in larger herds as a consequence of the mechanisation of process steps. In larger herds usually fewer qualified dairy personnel are available per cow and individual animals may hence be watched less intensively (VON KEYSERLINGK et al., 2009; SUNDRUM, 2015). Additionally, in larger herds more agonistic interactions among animals of different social ranks may take place and increase the risk of traumatic claw injuries and excessive standing times by subordinate animals (BARKER, 2007). This leads over to the fact that overstocking has to be taken into consideration as an important factor when assessing herd size and the association with lameness. KING et al. (2016) have identified a positive association between lameness and increasing stocking density. Excessive standing and walking times in overstocked pens is detrimental to claw health and triggers the development of foot lesions (BERGSTEN, 2001; BLOWEY, 2005; ESPEJO & ENDRES, 2007; RANDALL et al., 2015; ENDRES, 2017). Prolonged standing times impair blood circulation of the digital cushion which is dependent on pumping mechanisms ensured by foot load when walking. Anoxic conditions successively impede horn growth or result in a cessation of horn production.

Furthermore, agonistic interactions for resources, namely cubicles and feeding space, intensify in overstocked herds and lame cows happen to rest for a shorter period of time and stand or perch for a longer time instead (LEONARD et al., 1996; GALINDO & BROOM, 2000; FREGONESI et al., 2007; VON KEYSERLINGK, 2008; COOK & NORDLUND, 2009; VAN GASTELEN et al., 2011; ENDRES, 2017). Cows are subjected to fewer agonistic interactions, have an improved access to feed, and spend more time feeding when the availability of feed space is increased (FRIEND et al., 1977; DEVRIES et al., 2004; DEVRIES & VON KEYSERLINGK, 2006). Subordinate animals are at an especially high risk of experiencing the consequences of a high stocking rate, since they are less able to prevail against higher-ranking herd mates (WIERENGA & HOPSTER, 1990;

GALINDO & BROOM, 2000; GALINDO et al., 2000; HOHENBRINK & MEINECKE-TILLMANN, 2012; JENSEN et al., 2015). By implication, they experience permanent stress, loss of body condition, and health disorders such as lameness. Several studies have called for a number of spare cubicles to create the possibility for low-ranking cows to rest at any time (GALINDO & BROOM, 2000; GALINDO et al., 2000; ROUHA-MULLEDER et al., 2009).

2.2.4. Pasture access and presence of an outdoor exercise area

Grass represents the most suitable and natural surface for cattle to walk on and any available indoor flooring system remains inferior to the conditions on pasture. (GUARD, 2001; ALSAAOD et al., 2017). Pasture has positive effects on lameness dynamics and claw health within a herd and even a rather short period with pasture access remarkably accelerates the recovery of lame cows (HASKELL et al., 2006; HERNANDEZ-MENDO et al., 2007; ONYIRO et al., 2008; CHAPINAL et al., 2013; FABIAN et al., 2014). ADAMS et al. (2017) have observed lower lameness prevalences in pasture based husbandry systems compared with operations where cows did not have the possibility to spend time on pasture. The soft and frictional properties of natural sod surfaces enable cows to walk and stand more comfortably and easily (CAPION et al., 2008; CHAPINAL et al., 2013; ALSAAOD et al., 2017). Additionally, stocking densities are usually lower on pasture compared with indoor housing facilities (BARKER, 2007).

Access to additional outdoor exercise areas has been shown to be beneficial in regard to lameness as stocking density can hence be decreased (WELLS et al., 1995; ROUHA-MULLEDER et al., 2009). In tie stall operations, additional outdoor loafing areas help improving lameness problems and reduce the prevalence of sole disorders (BIELFELDT et al., 2005).

2.3. Cow level-associated risk factors

2.3.1. Body condition score

Several lines of evidence have indicated that low body condition is associated with an increased risk of lameness in dairy cows (BICALHO et al., 2009; LIM et al.,

2015; RANDALL et al., 2015; SOLANO et al., 2015; NEWSOME et al., 2017a; RANDALL et al., 2018). Following a 5-point scale with 0.25 increments (EDMONSON et al., 1989), cows with a BCS of ≤ 2.5 are twice as likely to be lame compared with cows ranging in BCS from 2.75 to 3.0 (ESPEJO et al., 2006; WESTIN et al., 2016b). Breed may well be of importance in the context of BCS, which is why a modification of the commonly implemented BCS scoring system by EDMONSON et al. (1989) has been presented in order to assess body condition in German Fleckvieh cattle (SCHÄFERS et al., 2002). However, most studies on the association of BCS with lameness have been conducted with cows of the Holstein Friesian dairy breed.

Non-infectious pathologies of the claw particularly appear to be initiated by low body condition (GREEN et al., 2014). It has been unravelled that thickness of the digital cushion is profoundly linked to body condition and decreases correspondingly to a decline in body condition (BICALHO et al., 2009; OIKONOMOU et al., 2014). Deeper structures, e.g. the corium, of the claw are hence less shielded from forces and pressure of weight-bearing (BICALHO et al., 2009; OIKONOMOU et al., 2013; NEWSOME et al., 2017a) and become more susceptible to damage and lameness-causing conditions such as sole ulcers and white line disease as a consequence of the disruption of claw horn growth. Furthermore, marked changes in body condition especially in the postpartum period add to and increased risk of lameness (HOEDEMAKER et al., 2009; ALAWNEH et al., 2014; LIM et al., 2015). RANDALL et al. (2015) have therefore suggested to keep cows at a BCS of at least 2.5 for the best results in reducing lameness.

Apart from that, an additional element regarding the association between low body condition and lameness may be a decreased feed intake in lame cows as they are either less able to compete with sound herd mates or modify their behaviour and spend a larger amount of time lying down (JUAREZ et al., 2003; HOEDEMAKER et al., 2009; BEER et al., 2016). The association of BCS and lameness may be part of a vicious circle and mutual causality seem rather reasonable in this context.

2.3.2. Milk yield

Constant genetic selection for high milk yield has entailed a considerable nutrient prioritisation for lactation to the tremendous disadvantage of dairy cow health,

physiology, and longevity (RAUW et al., 1998; LEROY et al., 2008; KNAUS, 2009; SUNDRUM, 2015). This creates a conflict of interests, since high yielding dairy cows are high risk candidates for metabolic imbalances, poor reproductive performance, and lameness (AMORY et al., 2008; ONYIRO et al., 2008; RUTHERFORD et al., 2009; ARCHER et al., 2010b; CHAPINAL et al., 2013; CHAPINAL et al., 2014; SOLANO et al., 2015). Unfavourable correlations between genetic predisposition for high milk yield and increased susceptibility to health disorders become even more pronounced in situations of insufficient management and husbandry (SUNDRUM, 2015). High yielding animals may have difficulties coping with housing conditions, require a longer time to be milked, and may have to change their feeding behaviour in order to increase feed intake secondary to the nutritive requirements induced by high yield (DELUYKER et al., 1991; COULON et al., 1996; BLOWEY, 2005; AMORY et al., 2008). RANJBAR et al. (2016) have demonstrated that every additional litre in average daily milk yield leads to an increase by 4% in the odds of being lame.

2.3.3. Parity and age

Older, multiparous cows are at an increased risk of lameness compared with younger, uniparous animals (WARNICK et al., 2001; SOGSTAD et al., 2005; ESPEJO et al., 2006; OIKONOMOU et al., 2013; FODITSCH et al., 2016; SOLANO et al., 2016a). These animals have obviously been confronted with the confined artificial environment they are housed in for a longer time and a cumulative effect of calving associated stress, endocrine and metabolic changes throughout parities and housing related deficiencies and their effect on energy balance and hoof structure may be detrimental to hoof conformation and claw health and add up to existing problems (SOLANO et al., 2015). Increasing age furthermore entails a reduced ability to cope with and adapt to deficient housing (KERR, 1998).

2.3.4. Stage of lactation

The initial four months after parturition represent a high risk period for lameness. Calving itself as well as husbandry changes and associated environmental and nutritional conditions challenge a cow’s ability to adapt (BARKEMA et al., 1994;

WHAY et al., 1997; WARNICK et al., 2001; SUNDRUM, 2015). Fifty percent of lameness cases occur during the first 120 DIM (ROWLANDS et al., 1985; SOLANO et al., 2016b). Also, laminitis most frequently challenges cattle during that time (SHEARER & VAN AMSTEL, 2017).

A heterogeneity of parameters interact and interrelate in the transition period and creates an elevated susceptibility to lameness (BLOWEY, 2005). Research has unravelled that the suspensory apparatus of the claw is subjected to biomechanical and histopathological changes and disruptions around the time of calving and the onset of lactation resulting in a compositional increase in elastin as well as decrease in proteoglycan within the corium and eventually leading to an increased laxity of the tissue and a higher softness of the claw's suspensory apparatus (TARLTON et al., 2002; TARLTON & WEBSTER, 2003; KNOTT et al., 2007). This is likely to be provoked by profound endocrine changes and metabolic modifications associated with calving and the onset of lactation. Elevated blood levels of delivery-related hormones, e.g. oestrogens and relaxin, induce collagen remodelling and have a loosening effect on collagenous and elastic filaments of the digital suspensory apparatus (BANI, 1997; SAMUEL et al., 1998; LISCHER, 2000; TARLTON et al., 2002; TARLTON & WEBSTER, 2003; KNOTT et al., 2007). Alterations in the structure of connective tissues supporting the third phalanx within the hoof capsule appear to coincide with profoundly elevated levels of matrix metalloproteinase-2 enzymes, matrix degrading proteases and markers for remodelling procedures, in the transition period (TARLTON & WEBSTER, 2003; KNOTT et al., 2007). As a consequence of the aforementioned processes, the suspensory apparatus becomes less resilient to stresses of weight bearing. The pedal bone enters a stadium of increased laxity and flexibility within the hoof capsule and may cause traumatic injuries of the corium and hence pain. Bruises of the corium may develop into sole ulcers and subsequently result in lameness.

3. Systematic reviews in medical literature

Clinicians are confronted with a cornucopia of complex problems and decision making related processes throughout their daily practise work (COOK et al., 1997; NAYLOR, 1997; BORENSTEIN et al., 2011; GOPALAKRISHNAN & GANESHKUMAR, 2013; PAGE et al., 2016). Health care decisions ought to be made based on the best available evidence from well-founded research. However, time is often scarce and difficulties arise staying abreast with the abundance of developments and knowledge generated by individual studies. In recent years, systematic reviews have become more and more important in medicine (MOHER et al., 2007; GOPALAKRISHNAN & GANESHKUMAR, 2013; PAGE et al., 2016). However, compared to the number of primary clinical studies, their number is relatively low (COOK et al., 1997; BRACKEN, 2013; POUND & BRACKEN, 2014).

Systematic reviews are of invaluable importance by summarising large bodies of evidence and exposing results, differences, and implications of primary research (COOK et al., 1997; GREEN, 2005; MOHER et al., 2007). They provide the possibility of a precise and organised appraisal and compilation of the state of knowledge by addressing a specific, sometimes narrow research question elaborately. In contrast, narrative reviews commonly elaborate on a broad field of interest related to a topic and are not able to present definite answers to the issue but rather are intended to give insights based on an underlying theory. Whereas articles are included based on the authors' decision in narrative reviews, systematic reviews define clear and reproducible procedures and apply explicit evidence-based criteria for the inclusion of studies in order to increase objectivity to the maximum extent possible (COOK et al., 1997; BORENSTEIN et al., 2011; GOPALAKRISHNAN & GANESHKUMAR, 2013). Developing a rigorous, clear, and precise protocol in advance and including a consistent reporting of information reduces the risk of introducing bias throughout the review process (COOK et al., 1997; GREEN, 2005; CENTRE FOR REVIEWS AND DISSEMINATION, 2009). The conduction of a systematic review is a step by step process (COOK et al., 1997; GREENHALGH, 1997; GREEN, 2005; MOHER et al., 2009; HIGGINS & GREEN, 2011). The research question should be formulated precisely and incorporate information on the population included, a specific setting, the condition

of interest, and objectives. A subsequent thorough literature research for all relevant articles results in a careful selection of studies following a predefined set of inclusion criteria both common to all studies as well as specific to the addressed field in order to assess the eligibility of the retrieved studies. As the quality of a systematic review is dependent on the scope and quality of the included studies, it is crucial to critically appraise the quality of the studies in a systematic and reproducible approach. Eventually, the collected information from the primary articles is aggregated and communicated through a qualitative, sometimes quantitative summary.

Not only are systematic reviews indispensable to communicate knowledge for medical and public health decision making, but also do they serve to establish clinical policy and identify areas of shortage of knowledge. Thus, they help future research to refine hypotheses, design studies, and expand their initiatives into certain directions (COOK et al., 1997; BORENSTEIN et al., 2011; GOPALAKRISHNAN & GANESHKUMAR, 2013). Since small single trials often lack generalisability due to the inclusion of particular populations, systematic reviews attempt to consider all studies on a specific research question and therefore aid at increasing generalisability and applicability based on a large body of available evidence (GREEN, 2005; PAGE et al., 2016).

4. The meta-analysis approach

Some systematic reviews may provide the possibility to retrieve studies that are similar and comparable in regard to their research hypothesis, population, and outcome. This further allows for a mathematical, quantitative compilation of effect sizes (GREENHALGH, 1997; BHANDARI et al., 2001; GREEN, 2005; RIED, 2006; GOPALAKRISHNAN & GANESHKUMAR, 2013). These systematic reviews are referred to as ‘meta-analyses’.

By implication, a meta-analysis is a powerful statistical tool to combine empirical data from related studies that summarises and presents evidence and creates transparent summary estimates for medical decision making (STEWART &

CLARKE, 1995; COOK et al., 1997; BORENSTEIN et al., 2011; RILEY et al., 2011; HARRIS et al, 2013). By compiling the deluge of data, the meta-analysis approach furthermore has the potential to provide definitive answers to clinical questions, resolve uncertainty and disagreement across studies, use available data efficiently, disentangle relationships, and frame guidelines and agendas for future research (COOK et al., 1997; EGGER & SMITH, 1997; BHANDARI et al., 2001; GOPALAKRISHNAN & GANESHKUMAR, 2013). Meta-analyses can be particularly helpful if inconsistencies are present among the results of primary studies (RIED, 2006; DALTON et al., 2016). Furthermore, the larger sample size within a meta-analysis enhances the power, generalisability, and precision of the outcome effect estimates.

In spite of the fact that systematic reviews, and even more meta-analyses increase the precision of an outcome and are regarded as the best evidence (GREEN, 2005; GOPALAKRISHNAN & GANESHKUMAR, 2013), they imply certain flaws that need to be taken into consideration, such as the selection of studies, the retrospective character that is always susceptible to bias, heterogeneity, loss of important information, and duplication of publication.

4.1. Fixed- versus random effects meta-analyses

For a correct interpretation of the results of a meta-analysis, it is important to be aware of the model that has been implemented (RILEY et al., 2011).

Random effects meta-analyses provide the average effect estimate across all studies within the approach and acknowledge that effects may differ due to different settings in individual studies (RIED, 2006; RILEY et al., 2011). Furthermore, potential heterogeneity among studies is taken into account. The percentage of heterogeneity within a meta-analysis, i.e. the value of I^2 or τ^2 as the variance between studies hence give an indication of the variability in effect estimates as a consequence of actual study differences rather than chance (BORENSTEIN et al., 2011; RILEY et al., 2011). These may reflect differences in individual settings, populations and other factors or chance in regard to sampling. Even an infinite sample size would result in varying study effects observed due to real differences.

By contrast, fixed effects meta-analyses operate on the assumption that equal

effects sizes are shared by all studies and no heterogeneity is present between the individual studies (BORENSTEIN et al., 2011; RILEY et al., 2011; CHEUNG, 2015). This further entails the implication that potential variations are solely due to chance differences attributable to the sampling process. Accordingly, if an infinite sample size underlay all included studies, no differences as a result of chance would arise. In a fixed effect meta-analysis, I^2, the percentage of variability in effect estimates across studies due to an actual heterogeneity of studies rather than chance, is zero percent.

Fixed effects models are adequate when a small number of well-controlled, functionally equivalent studies with identical features are synthesised rather than all potential studies (BORENSTEIN et al., 2011; CHEUNG, 2015). It is not intended to generalise to populations, but to calculate effect sizes for a specifically identified population. In the case of a random effects meta-analysis, study-specific random effects are acknowledged. On an individual study basis, a certain effect may be different from the average effect estimate across all possible studies. However, since random effects meta-analyses regard the presence of frequently unexplained heterogeneity, they have been the most common approach in a medical context (RILEY et al., 2011).

4.2. The problem of bias

Due to their retrospective character, systematic reviews are naturally prone to the introduction of bias in the course of their completion (GREEN, 2005; GOPALAKRISHNAN & GANESHKUMAR, 2013). This is even more important to consider as the quality of systematic reviews is dependent in the quality of the primary studies they incorporate (MOHER et al., 2009; HARRIS et al., 2013). Besides the collation and combination of outcomes from similar and comparable studies, systematic reviews and meta-analyses make an attempt to set limits on the bias introduced by individual trials. Publication bias has been defined as the tendency of researchers, reviewers, editors, and sponsors to preferably publish study outcomes based on the kind of results, i.e. mainly those results that are statistically or clinically significant (SONG et al., 2010; KICINSKI et al., 2015; SEDGWICK, 2015; DALTON et al., 2016; EKMEKCI, 2017). Unpublished research may also be caused by lack of time, insignificant results, and conflict of

interests. It is yet paramount to understand that bias in primary research can arise in multifarious forms: Outcome reporting bias, time-lag bias, language bias, citation bias, multiple publication bias, and data base indexing bias. 'Outcome reporting bias' refers to the problem that statistically significant outcomes are clearly favoured for publication whereas negative, i.e. statistically not significant results are neglected. 'Time-lag bias' means that the study outcomes have a considerable influence on the time from submission to publication. Consequently, research with significant or important results is published more quickly. In spite of the fact that most knowledge happens to be published in English, a substantial percentage of literature is only available in languages other than English. Including articles that are accessible in English only introduces a particular language bias to the systematic review. As outlined, significant outcomes tend to be published more frequently and are also favoured when it comes to the duration of the review process. Additionally, statistically significant results tend to be cited more often and the impact factor of the journal, the researchers involved, their nationality, and the language of publication add up to the problem referred to as 'citation bias'. This selective citation may create the illusion of an enhanced importance of the cited study. In some cases, several publications including various hypotheses, methodology, or outcomes may be published on the basis of the same single data set or population. Notwithstanding the redundant publication, the perception may thereby be raised that the results can be traced back to individual settings and the outcomes are hence overemphasised (JOHNSON, 2006). Hence, 'multiple publication bias' has occurred. At last, data base indexing bias is a form of bias where major electronic resources may not index all available studies in a field. This is due to the fact that the majority of journals included in the main data bases is from Western countries. Attention may therefore be drawn away from other relevant articles in a field which are not indexed in these data bases.

In addition to the bias of individual studies, another critical source of bias in a systematic review may be caused by methodological flaws or limitations. Bias can arise at all stages of the step-by-step review process (SONG et al., 2010; WHITING et al., 2016; EKMEKCI, 2017) and it is therefore substantial to minimise bias on various levels. MOHER et al. (2009) have endorsed an a-priori registration of the review protocol in order to assure transparency as well as to reduce the potential of duplication. Furthermore, the quality of conduct and eventual reporting of a review

is hence enhanced and the risk of bias can be reduced (SHEA et al. 2007; HARRIS et al., 2013). A flow chart in accordance with the PRISMA principles visualises the step-by-step process of literature research, inclusion and exclusion of retrieved articles, analysis, and presentation of finally incorporated studies. Inclusion criteria for the eligibility of studies ought to be specified prior to starting a systematic review even though these may be modified throughout the study selection process. The search strategy itself should aim attention at information on the PICO criteria: participants/population, interventions, comparisons, and outcome. A broad literature search can be achieved by scrutinising a minimum of two electronic data bases. Once the screening of studies has started, it has been recommended that two reviewers at least should be involved in the scrutiny of primary articles, the application of inclusion criteria, and the extraction of data (SHEA et al., 2007; HARRIS et al., 2013. In the case of disagreement on the eligibility of an article, a third investigator ought to be contacted to decide upon inclusion. As previously outlined, the quality of a systematic review is only as good as the quality of primary studies it incorporates (HARRIS et al., 2013). However, when speaking of the quality of primary investigations, the quality of reporting in these articles is evaluated more than the quality of their performance itself. Quality evaluation tools as well as checklists to appraise the quality of reporting in primary studies are mainly intended to assess bias, selection, performance, and study design of primary investigations (VON ELM et al., 2007; HARRIS et al., 2013). Equivalently, several tools have been designed in order to assess the methodology and methodological quality of systematic reviews as well as the potential risk of bias (SHEA et al., 2007; MOHER et al., 2009; WHITING et al., 2016). SHEA et al. (2007) have presented AMSTAR, probably the most common quality assessment tool for systematic reviews that provides a checklist consisting of 11 elements that appear to be critical when checking the methodological quality of systematic reviews. These elements include the provision of an a priori design, duplicate study selection, comprehensive literature research and other important steps throughout a review process. Similarly, MOHER et al. (2009) have collated a list of items to consider in the reporting of systematic reviews or meta-analyses. More recently, the ROBIS tool has been introduced to assess the risk of bias in systematic reviews. This incorporates the PICO terms, the identification of points where potential bias may have been introduced into the review, and the consideration whether or not the review itself is at risk of bias.

When performing a meta-analysis, bias can additionally be addressed by performing a funnel plot analysis to detect publication bias or to answer the question if studies with a small sample size give results that differ from studies with larger sample sizes as well as by choosing a forest plot to graphically illustrate the summary estimate of effects for the included studies (WRIGHT et al., 2007; HARRIS et al., 2013; JIN et al., 2015; CHOI et al., 2016; DALTON et al., 2016). The latter kind of graph also displays the relative strength of each single study within the analysis. Additionally, a biostatistician experienced in the conduct of meta-analyses is recommended to be involved.

III. MATERIAL AND METHODS

This systematic review and meta-analyses were conducted following a pre-specified study protocol in compliance with the procedures presented by SHAMSEER et al. (2015) (see Appendix Section 4).

1. Search strategy and selection criteria

Three commonly implemented quality assessment tools for systematic reviews and meta-analyses, i.e. AMSTAR, PRISMA, and ROBIS, were taken into consideration throughout the course of this study (SHEA et al., 2007; MOHER et al., 2009; WHITING et al., 2016).

A professional librarian experienced with electronic sources conducted an extensive literature research for all available years from inception up to February 27, 2018, using the search engines MEDLINE (incl. Epub ahead of print, In process and other non-indexed citations), Web of Science, BIOSIS Previews, AGRICOLA, VETMED RESOURCE/CABI.

The search terms listed below were applied to extract as many potentially relevant articles as possible from the electronic sources. The search terms were separated into four components in correspondence with the elements of this review: risk factors, lameness, dairy cows. Alternative wording was permitted for each of these components, indicated by the operator “OR” and every component was combined with the others by the separator “AND”. An asterisk indicates that the data base will be scrutinised for words beginning with these letters.

1) To identify studies with a study population of animals in the dairy sector exclusively. Alternatively to “dairy cow”, other wording was permitted by the operator “OR”.

a. ("dairy cow" OR "dairy cows" OR "dairy farm" OR "dairy farms" OR "dairy herd" OR "dairy herds" OR "dairy cattle") **AND:**

2) To identify studies with the relevant outcome of lameness. Alternative wording was permitted by the operator “OR”.

a. (lame* OR ((impaired OR alter* OR disturb*) **AND:**

3) To identify all possibly relevant studies describing locomotion characteristics.

a. (gait OR locomotion))) **AND:**

4) To identify studies describing various factors associated with lameness. Alternative wording was permitted by the operator “OR”.

a. (((risk OR management OR "herd-level") **AND** factor*) OR prevalence OR associat*)

2. Study selection

Initially, studies of all designs and of all languages describing risk factors for lameness in dairy cows and alternative wording were admitted according to the search terms. Subsequently, studies which were not written or available in Dutch, English, French, German, Italian, Portuguese or Spanish were excluded from further assessment as well as publications that were not accessible by any means. Full texts were subjected to screening and only those studies were included where

animals were kept in free stall facilities or tie stall operations. This means that investigations where dairy cows were housed in pasture based systems or deep-bedded packs were excluded from this systematic review.

After exclusion of duplicate studies, two reviewers independently examined titles and abstracts of all remaining publications in compliance with the eligibility criteria. When disagreement about the eligibility of an article arose, a third investigator was consulted to decide upon inclusion. Where a study appeared to be eligible, the full text was obtained and examined for eligibility one more time. The reporting quality of each study was assessed using the STROBE checklists (VON ELM et al, 2007). Non-primary studies, conference abstracts or book sections as well as studies that did not comply with at least 15 of the 22 listed criteria (cf. IX.7) in these guidelines were excluded from subsequent scrutiny.

3. Data extraction

Information was extracted regarding author and publication date, country, risk factors for lameness in dairy cows, definition of lameness and applied locomotion scoring system, number of animals, housing system and funding of the research project. Type of extracted information had been previously specified in consultation with a biostatistician and an epidemiologist. When relevant data were missing, the corresponding author was contacted to access further information.

4. Statistical analysis

Data were extracted and collected using a single electronic form containing information on author(s), study title, year of publication, country, group sizes i.e. absolute number or percentage of lame and sound animals with regard to different risk factors, confidence intervals, standard errors of odds ratios, and coefficients, odds ratios and p-values using Microsoft Excel 2016 (macOS). A meta-analysis was performed if sufficient and usable data on a risk factor could be collected from a primary study or from the corresponding author(s) in case the information was not available in the retrieved original article.

The R-package "meta" was applied in all meta-analyses for the following variables: BCS, DIM, claw overgrowth, herd size, and parity (R DEVELOPMENT CORE TEAM, 2017; SCHWARZER, 2007). The random effects model was chosen due to the underlying heterogeneity in population characteristics. The R function "metagen" was used to generate pooled estimates which were visualised in forest plots. Forest plots incorporated information on the OR and the 95% confidence interval of the summary effects. The shaded box represents the relative contribution of each study to the summary OR. Publication bias was assessed by creating funnel plots for each single meta-analysis using the R function 'funnel'.

Log(OR), standard errors of coefficients, and the number of lame and sound animals in each category of the risk factor were used in all meta-analyses. Coefficients (log(OR)) were extracted directly from the articles or obtained by means of transforming the reported odds ratios with natural logarithm. If information on standard error was not available in a particular paper, the value was calculated from confidence interval limits if reported. Confidence intervals around the coefficients were used directly for 95% and 90% confidence intervals according to HIGGINS and GREEN (2011):

$$SE = \frac{\text{upper limit} - \text{lower limit}}{3.92}$$

Formula 1: Calculation of standard error from 95% confidence intervals

$$SE = \frac{\text{upper limit} - \text{lower limit}}{3.29}$$

Formula 2: Calculation of standard error from 90% confidence intervals

For BCS, only studies that included cows of the Holstein-Friesian breed, were incorporated. The reference category had to be changed to a reference category different from the original category in KING et al. (2017). The scoring system suggested by EDMONSON et al. (1989) has been widely used across studies. A BCS of ≤ 2.5 was determined as the reference category according to the majority of studies about BCS and lameness and calculated odds ratios and standard errors for the other categories of BCS 3.0 and BCS ≥ 3.5, respectively, compared with a BCS of ≤ 2.5:

$$\text{OR}_{\text{BCS 3.0}} = \frac{\text{OR}_{\text{BCS 3.0}}(\text{old reference category})}{\text{OR}_{\text{BCS} \leq 2.5}(\text{new reference category})}$$

Formula 3: Calculation of OR for a BCS of 3.0 compared with a BCS of ≤2.5 given the old reference category of BCS 3.0

$$\text{OR}_{\text{BCS} \geq 3.5} = \frac{\text{OR}_{\text{BCS} \geq 3.5}(\text{old reference category})}{\text{OR}_{\text{BCS} \leq 2.5}(\text{new reference category})}$$

Formula 4: Calculation of OR for a BCS ≥ 3.5 compared with a BCS of ≤2.5 given the old reference category of BCS ≥3.5

The standard error was calculated as the square root from values obtained applying the following procedure:

$$SE = \sqrt{\frac{1}{n_{\text{sound BCS 3.0}}} + \frac{1}{n_{\text{lame BCS 3.0}}} + \frac{1}{n_{\text{sound BCS}\leq 2.5}} + \frac{1}{n_{\text{lame BCS}\leq 2.5}}}$$

Formula 5: Calculation of the standard error as the square root from obtained values for the number (n) of lame and sound animals both for BCS ≤2.5 and a BCS of 3.0

and

$$SE = \sqrt{\frac{1}{n_{\text{sound BCS 3.5}}} + \frac{1}{n_{\text{lame BCS 3.5}}} + \frac{1}{n_{\text{sound BCS}\leq 2.5}} + \frac{1}{n_{\text{lame BCS}\leq 2.5}}}$$

Formula 6: Calculation of the standard error as the square root from obtained values for the number (n) of lame and sound animals both for BCS ≤2.5 and a BCS of 3.5

If odds ratios had to be pooled, the Mantel-Haenszel method was implemented (BORENSTEIN et al., 2011):

$$\text{OR}_i = \frac{A_i D_i}{C_i B_i}$$

Formula 7: Mantel-Haenszel method to compute odds ratios from events by risk factor. OR_i denotes the odds ratio in a study *i*. A, B, C, D represent the numbers of animals in each group of risk factor (Table 1). Accordingly, A_i refers to the number of lame animals for a certain risk factor (e.g. parity 2) in a study *i*, whereas B_i refers to the number of lame animals within the reference category (e.g. parity 1). D_i and C_i denote the numbers of non-lame animals for a certain risk factor (e.g. parity 2) and within the reference category (e.g. parity 1).

Table 1. Nomenclature for 2 x 2 table of lame/non-lame cows by risk factor (BORENSTEIN et al., 2011) for the data of each study. Each letter represents the number of lame or sound animals in each group according to a certain risk factor.

	Risk factor	**Reference category of risk factor**	**Total number of animals**
Number of animals (lame)	A	B	n_1
Number of animals (non-lame)	C	D	n_2

Weight was assigned to each study.

$$W_i = \frac{B_i C_i}{n_i^1}$$

Formula 8: The Mantel-Haenszel method assigns weight (W_i) to each study where $n_i = A_i + B_i + C_i + D_i$.

and the Mantel-Haenszel odds ratio (OR_{MH}) then computed as

$$\mathrm{OR}_{\mathrm{MH}} = \frac{\sum_{i=1}^{k} W_i OR_i}{\sum_{i=1}^{k} W_i}$$

Formula 9: Computation of the Mantel-Haenszel odds ratio (OR_{MH}).

Furthermore in this context, standard errors were produced by calculating the square root of the variance *V*. The Mantel-Haenszel approach requires to produce single values for each study, which will then be computed to obtain the variance of

the summary effect for each study (*i*):

$$\mathrm{R}_i = \frac{A_i D_i}{n_i}$$

$$S_i = \frac{B_i C_i}{n_i}$$

$$E_i = \frac{\left(A_i + D_i\right) A_i D_i}{n_i^2}$$

$$F_i = \frac{\left(A_i + D_i\right) B_i C_i}{n_i^2}$$

$$G_i = \frac{\left(B_i + C_i\right) A_i D_i}{n_i^2}$$

$$H_i = \frac{\left(B_i + C_i\right) B_i C_i}{n_i^2}$$

Formula 10: Single values are produced for each study (R_i, S_i, E_i, F_i, G_i, H_i) in order to subsequently calculate the variance of the summary effect for each study.

Since the variance is computed in log units, the odds ratio can be transformed into log units (BORENSTEIN et al., 2011):

$$\ln \mathrm{OR}_{MH} = \ln\left(\mathrm{OR}_{MH}\right)$$

Formula 11: Transformation of the Mantel-Haenszel odds ratio (OR_{MH}) into log units where ln denotes the natural logarithm of the Mantel-Haenszel OR.

Then the variance is yielded eventually by

$$V_{\ln OR_{MH}} = \left(\frac{\sum_{i=1}^{k} E_i}{\left(\sum_{i=1}^{k} R_i\right)^2} + \frac{\sum_{i=1}^{k} F_i + \sum_{i=1}^{k} G_i}{\sum_{i=1}^{k} R_i \times \sum_{i=1}^{k} S_i} + \frac{\sum_{i=1}^{k} H_i}{\left(\sum_{i=1}^{k} S_i\right)^2} \right)$$

Formula 12: Calculation of the variance

$$SE_{\ln \mathrm{OR}_{MH}} = \sqrt{V_{\ln OR_{MH}}}$$

Formula 13: Calculation of the standard error as square root from the previously yielded variance

IV. RESULTS

1. Systematic review

A PRISMA flow chart was generated in order to present an overview of literature search and study selection at various stages of the review process (Figure 1). Literature research of five electronic sources yielded a pool of 3608 references altogether of which 1941 remained within the analysis after deduplication (Table 2). A total number of 1613 publications were excluded on the basis of their title, the abstract of 26 articles was not available and three publications had to be excluded due to language difficulties (Japanese, Polish, Turkish). Subsequently, abstracts of 299 remaining articles could be examined, whereby 25 were not accessible by any means and 102 were excluded. Full texts of 172 publications were hence thoroughly reviewed which left 120 articles for the assessment of reporting quality using the STROBE checklists (VON ELM et al., 2007). In the end, 53 studies remained to be included in the systematic review (Appendix, Table 5). Within these, 128 risk factors associated with lameness in dairy cows were identified (Table 3).

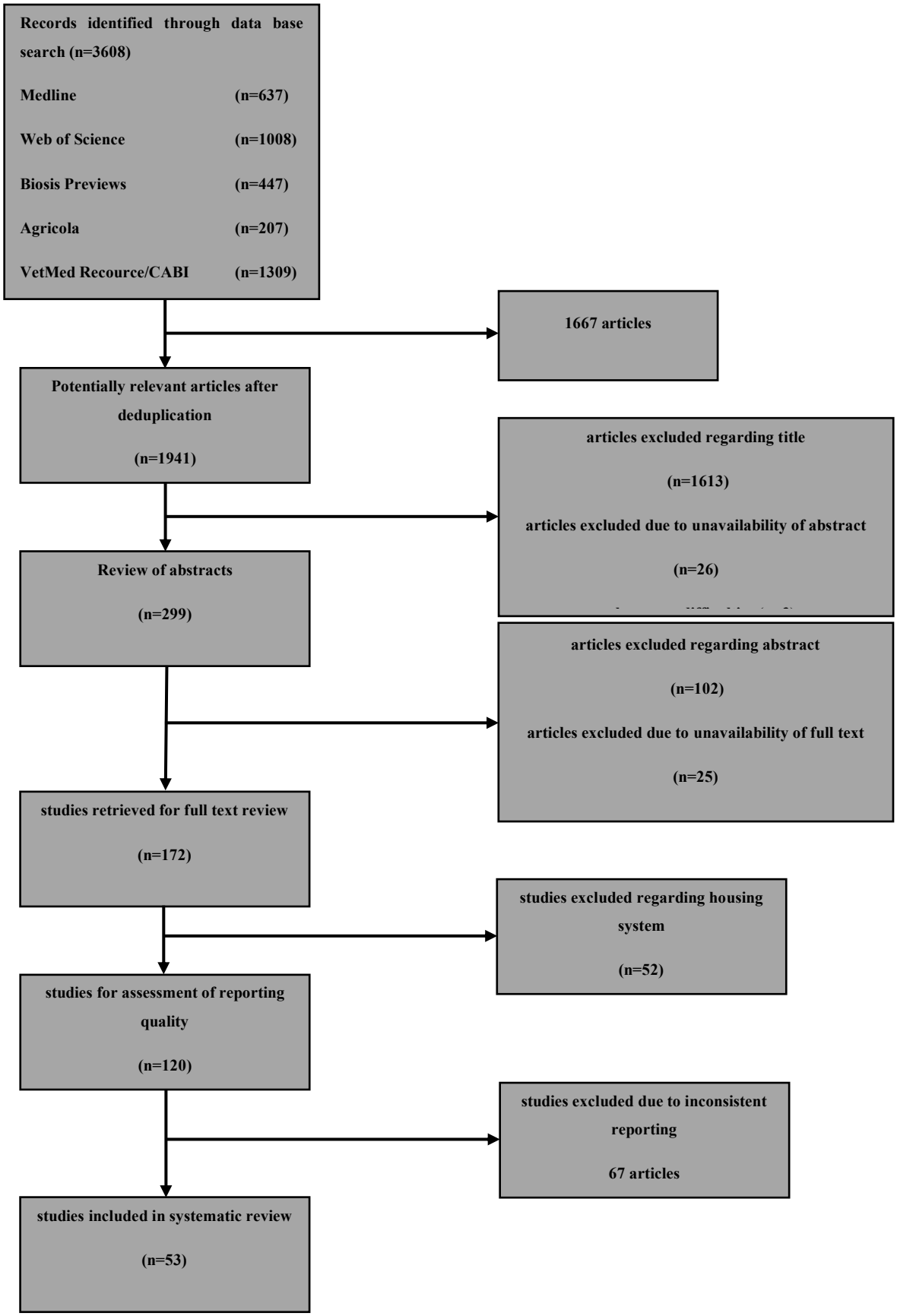
Records identified through data base search (n=3608)
Medline (n=637)
Web of Science (n=1008)
Biosis Previews (n=447)
Agricola (n=207)
VetMed Recource/CABI (n=1309)
1667 articles
Potentially relevant articles after deduplication
(n=1941)
articles excluded regarding title
(n=1613)
articles excluded due to unavailability of abstract
(n=26)
Review of abstracts
(n=299)
articles excluded regarding abstract
(n=102)
articles excluded due to unavailability of full text
(n=25)
studies retrieved for full text review
(n=172)
studies excluded regarding housing system
(n=52)
studies for assessment of reporting quality
(n=120)
studies excluded due to inconsistent reporting
67 articles
studies included in systematic review
(n=53)

Figure 1: PRISMA flowchart visualising the study selection process throughout the review. Out of the 3608 articles, that were detected initially, 1941 were retrieved for further analysis. Scrutiny of titles lead to the exclusion of 1613 papers. For 26 articles, the abstract was not accessible and 3 articles were excluded due to language difficulties. This left 299 publications to abstract review. 102 articles were excluded in this context and 25 more, because full text was not available. Full text review could hence be performed for 172 studies and lead to the exclusion of 52 publications, since cows in these studies were not housed in free stall- or tie stall facilities. The STROBE checklists (STROBE statement, 2007) were used to appraise methodological quality of 120 studies. 67 non-quantitative studies, book sections and narrative reviews were excluded. 53 studies were retrieved for the systematic review

Table 2: Number of extracted papers per data base

Data Base	Deduplication	
	Before	After
MEDLINE (incl. Epub ahead of print, In process & other non-indexed citations	637	192
Web of Science	1008	990
Biosis Previews	447	45
AGRICOLA	207	11
VETMED RESOURCE/CABI (https://www.cabi.org/VetMedResource/)	1309	703
Pool	3608	1941

Table 3: Factors associated with lameness in dairy cows. [1]The term 'stall base' has been used ambiguously. Several studies regarded it as a synonym to 'bedding'. Other studies did not follow that interpretation and referred to the composition of the surface beneath the bedding itself. Both terms are displayed separately.

Risk factor	Study
Parity	Alban et al., 1996 Alban L., 1995 Boettcher et al., 1998 Dippel et al., 2009a Dippel et al., 2009b Espejo et al., 2006 Foditsch et al., 2016 Green et al., 2014 Groehn et al., 1992 Hedges et al., 2001 Hultgren et al., 2007 King et al., 2017 Manske, 2002b
Parity	Manske, 2002c Morabito et al., 2017 Newsome et al., 2017b O'Driscoll et al., 2009 Potzsch et al., 2003 Sadiq et al., 2017 Sarjokari et al., 2013 Sogstad et al., 2005 Solano et al., 2015 Weber et al., 2013 Wells et al., 1993 Westin et al., 2016b Yaylak et al., 2010
BCS	Becker et al., 2014 Dippel et al., 2009a Dippel et al., 2009b

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
BCS	Foditsch et al., 2016 Green et al., 2014 Gudaj et al., 2012 King et al., 2017 Morabito et al., 2017 Onyiro et al., 2008 Ristevski et al., 2017a Ristevski et al., 2017b Sadiq et al., 2017 Solano et al., 2015 Wells et al., 1993 Westin et al., 2016b Yaylak et al., 2010
DIM	Boettcher et al., 1998 Espejo et al., 2006 Green et al., 2014 Manske, 2002b
DIM	Manske, 2002c Morabito et al., 2017 Pérez-Cabal et al., 2014 Sadiq et al., 2017 Weber et al., 2013 Wells et al., 1993
Herd size	Adams et al., 2017 Alban L., 1995 Chapinal et al., 2014 Chapinal et al., 2013 Dippel et al., 2009b Faye et al., 1989 Groehn et al., 1992 Solano et al., 2015 Westin et al., 2016b Yaylak et al., 2010

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Flooring surface type (concrete, rubber etc.)	Adams et al., 2017 Faye et al., 1989 Frankena et al., 2009 Hettich et al., 2007 Hultgren et al., 2007 Manske, 2002b Manske, 2002c Rouha-Mulleder et al., 2009 Wongsanit et al., 2015
Bedding type	Adams et al., 2017 Chapinal et al., 2014 Chapinal et al., 2013 Cook et al., 2016 Groehn et al., 1992 Pérez-Cabal et al., 2014 Rouha-Mulleder et al., 2009
Flooring type (slatted, solid)	Adams et al., 2017 Dippel et al., 2009b Frankena et al., 2009 Hultgren et al., 2007 Pérez-Cabal et al., 2014 Rouha-Mulleder et al., 2009 Sarjokari et al., 2013
Frequency of claw trimming	Adams et al., 2017 Becker et al., 2014 Espejo et al., 2007 Manske,2002b Pérez-Cabal et al., 2014 Wongsanit et al., 2015
Milk yield	Battagin et al., 2013 Green et al., 2014 Green et al., 2010 Pérez-Cabal et al., 2014 Ristevski et al., 2017b

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Milk yield	Solano et al., 2015
Stall surface/base[1]	Andreasen and Forkman., 2012 Cook, 2003 Dippel et al., 2009a Dippel et al., 2009b Solano et al., 2015 Westin et al., 2016b
Availability of outside exercise area	Adams et al., 2017 Becker et al., 2014 Dippel et al., 2009b Rouha-Mulleder et al., 2009 Wells et al., 1995b
Claw overgrowth	Dembele et al., 2006 Morabito et al., 2017 Sadiq et al., 2017 Solano et al., 2015 Wells et al., 1993
Season	Cook, 2003 Foditsch et al., 2016 Green et al., 2014 Groehn et al., 1992 Onyiro et al., 2008
Housing type	Adams et al., 2017 Groehn et al., 1992 Pérez-Cabal et al., 2014 Wongsanit et al., 2015
Presence of footbath	Adams et al., 2017 Gudaj et al., 2012 Hettich et al., 2007 Pérez-Cabal et al., 2014
Stall width	Bouffard et al., 2017 Dippel et al., 2009b Sogstad et al., 2005

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Stall width	Westin et al., 2016b
Access to pasture	Chapinal et al., 2013 Pérez-Cabal et al., 2014 Wells et al., 1995b
Bedding quantity	Morabito et al., 2017 Solano et al., 2015 Westin et al., 2016b
Floor slipperiness	Dembele et al., 2006 Sarjokari et al., 2013 Solano et al., 2015
Frequency of manure removal	Chapinal et al., 2013 King et al., 2016 Yaylak et al., 2010
General cleanliness	Becker et al., 2014 Dembele et el., 2006 Sadiq et al., 2017
Milk protein content	Battagin et al., 2013 Dippel et al., 2009b Pérez-Cabal et al., 2014
Neck rail distance to rear curb	Chapinal, 2013 Dippel et al., 2009a Rouha-Mulleder et al., 2009
Presence of hock injuries	Morabito et al., 2017 Solano et al., 2015 Westin et al., 2016b
Breed	Alban L., 1995 Sarjokari et al., 2013
Brisket board height	Espejo et al., 2007 Westin et al., 2016b
Calving season	Alban et al., 1996 Alban L., 1995
Kerb height	King et al., 2016 Rouha-Mulleder et al., 2009

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Length of stalls	Faye et al., 1989 Wells et al., 1995b
Lunge space obstruction	Dippel et al., 2009a Westin et al., 2016b
Milk fat content	Battagin et al., 2013 Pérez-Cabal et al., 2014
Occurrence of previous lameness	Green et al., 2014 Hirst et al., 2002b
Pen area available per cow	Westin et al., 2016b Yaylak et al., 2010
Presence of rubber mats in walkways	Adams et al., 2017 Chapinal et al., 2013
Stocking density	King et al., 2016 Westin et al., 2016b
Supplementation of biotin	Hedges et al., 2001 Potzsch et al., 2003
Temperature	King et al., 2017 King et al., 2016
Width of feed alley	Sarjokari et al., 2013 Westin et al., 2016b
Abnormal lying behaviour	Dippel et al., 2009b
Angularity	Battagin et al., 2013
Animal keeper is owner	Yaylak et al., 2010
Animal keeper is stockman	Yaylak et al., 2010
Area behind brisket board filled with concrete	Espejo et al., 2007
Availability of feeding expert	Yaylak et al., 2010
Barn age	Chapinal et al., 2014
Bedding cleanliness	Gudaj et al., 2012
Blood BHBA	Ristevski et al., 2017b
Blood LDH	Ristevski et al., 2017b
Blood Triglycerides	Ristevski et al., 2017b
Body weight	Wells et al., 1993
Breed class	Becker et al., 2014

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Changing diet prior to calving	Hettich et al., 2007
Cleanliness of udder	Becker et al., 2014
Cleanliness of flank	Becker et al., 2014
Cleanliness of legs	Westin et al., 2016b
Consideration of claw health in breeding	Becker et al., 2014
Cow care quality	Dembele et al., 2006
Cow comfort	Espejo et al., 2007
Cow trainer use routine	Alban et al., 1996
Diagnosis season of lameness event	Pérez-Cabal et al., 2014
Distribution of maize silage	Faye et al., 1989
Duration of cow-calf contact	Rouha-Mulleder et al., 2009
Duration of rising process	Dippel et al., 2009b
Farmer's expectation to be farmer in 5 years	Alban L., 1995
Farmer's opinion of importance of claw health	Becker et al., 2014
Feed barrier type	Sarjokari et al., 2013
Feeding corn silage in spring	Wells et al., 1995b
Feeding dry concentrate in summer	Wells et al., 1995b
Feeding dry hay	Groehn et al., 1992
Feeding fresh forage in summer	Wells et al., 1995b
Feeding hay in spring	Wells et al., 1995b
Feeding haylage in spring/summer	Wells et al., 1995b
Feeding silage	Becker et al., 2014
Feeding space available per cow	Westin et al., 2016b
Feeding wet concentrate in summer	Wells et al., 1995b
Free stall care	Morabito et al., 2017
Frequency of footbath	Chapinal et al., 2013
Frequency of raking stalls	Westin et al., 2016b
Frequency of ration balancing	Wells et al., 1995b
Frequency of visits by hoof trimmer	Adams et al., 2017
Gutter width	Wells et al., 1995b
Herd milk yield	Alban et al., 1996
Hock condition score	Sadiq et al., 2017
Hours/day spent in free stalls	Wells et al., 1995b

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Hours/day spent in stanchions	Wells et al., 1995b
Hours/day spent in tie stalls	Wells et al., 1995b
Implementation of cow comfort assessment	Morabito et al., 2017
Length of lying area	Dippel et al., 2009b
Long-term administration of sometribove (methionyl bovine somatotropin, 500mg, sc.)	Wells et al., 1995a
Manure removal strategy	Hultgren et al., 2007
Number of cows per milking robot	Westin et al., 2016b
Milking cows that are obviously ill	Gudaj et al., 2012
Number of lactating cows	Wells et al., 1995b
Number of stalls	Gudaj et al., 2012
Percentage of fat cows	Rouha-Mulleder et al., 2009
Percentage of stalls with fecal contamination	Chapinal et al., 2013
Polymorphism at STAT5A and FGF2 gene loci	Oikonomou et al., 2011
Position of neck rail	Bernardi et al., 2009
Position of tie-rail	Bouffard et al., 2017
Presence and condition of stalls with dividers	Wells et al., 1995b
Presence of deep swelling on limbs	Wells et al., 1993
Presence of fans	Adams et al., 2017
Presence of feed stalls	Hultgren et al., 2007
Presence of infection on limbs	Wells et al., 1993
Presence of knee injuries	Westin et al., 2016b
Presence of laceration on limbs	Wells et al., 1993
Presence of skin lesions	Dembele et al., 2006
Presence of sprinklers	Adams et al., 2017
Presence of superficial swelling on limbs	Wells et al., 1993
Presence of synovial swelling on limbs	Wells et al., 1993
Previous lactation claw horn disruption lesion-incidence	Foditsch et al., 2016
Promptness of treatment for lameness	Adams et al., 2017
Proportion of cows in cubicles that are lying down	Dippel et al., 2009b

Table 3 (continued): Factors associated with lameness in dairy cows.

Risk factor	Study
Ratio of concentrate feed to total feed	Yaylak et al., 2010
Rear lateral claw angle	Wells et al., 1993
Rearing replacement heifers on site	Chapinal et al., 2013
Soil area available per cow	Yaylak et al., 2010
Sole soft tissue thickness	Newsome et al., 2017b
Surface moisture	Adams et al., 2017
Thickness of fat over tuber ischiadicum	Ristevski et al., 2017a
Tie rail height	Bouffard et al., 2017
Tie system	Alban et al., 1996
Time away from pen	Espejo et al., 2007
Time of claw trimming	Manske, 2002c
Type of water supply	Sarjokari et al., 2013
Water linear space per cow	Chapinal et al., 2013
Width of entranceway	Wells et al., 1995b
Within-herd prevalence of digital dermatitis and heel-horn erosion	Becker et al., 2014

2. Meta-analyses

Table 4 gives an overview of risk factors and studies that were included in meta-analyses.

Table 4: Risk factors and studies included in meta-analyses.

Risk factor	Author(s)	Year	Study
BCS	King et al.	2017	Cow-level associations of lameness, behavior, and milk yield of cows milked in automated systems.
	Solano et al.	2015	Prevalence of lameness and associated risk factors in Canadian Holstein-Friesian cows housed in freestall barns

Table 4 (continued): Risk factors and studies included in meta-analyses.

Risk factor	Author(s)	Year	Study
Claw overgrowth	Sadiq et al.	2017	Prevalence of lameness, claw lesions, and associated risk factors in dairy farms in Selangor, Malaysia
	Solano et al.	2015	Prevalence of lameness and associated risk factors in Canadian Holstein-Friesian cows housed in freestall barns
DIM	Sadiq et al.	2017	Prevalence of lameness, claw lesions, and associated risk factors in dairy farms in Selangor, Malaysia
	Manske	2002	Hoof lesions and lameness in Swedish dairy cattle: prevalence, risk factors, effects of claw trimming, and consequences for productivity
Herd size	Yaylak et al.	2010	The effects of several cow and herd level factors on lameness in Holstein cows reared in Izmir Province of Turkey
	Alban, L.	1995	Lameness in Danish dairy cows: frequency and possible risk factors
Parity	King et al.	2017	Cow-level associations of lameness, behavior, and milk yield of cows milked in automated systems
	Sadiq et al.	2017	Prevalence of lameness, claw lesions, and associated risk factors in dairy farms in Selangor, Malaysia
	Solano et al.	2015	Prevalence of lameness and associated risk factors in Canadian Holstein-Friesian cows housed in freestall barns
	Yaylak et al.	2010	The effects of several cow and herd level factors on lameness in Holstein cows reared in Izmir Province of Turkey
	Manske	2002	Hoof lesions and lameness in Swedish dairy cattle: prevalence, risk factors, effects of claw trimming, and consequences for productivity
	Alban, L.	1995	Lameness in Danish dairy cows: frequency and possible risk factors

A BCS of ≤ 2.5 was regarded as reference category and scores of 3.0 and ≥ 3.5 were compared with this. Cows with a BCS of 3.0 show a decreased risk (OR 0.73; CI

0.54 – 0.98) to develop lameness compared with those animals in the reference category (Figure 2) and cattle with a condition score of ≥ 3.5 are at lowest risk of lameness (OR 0.55; CI 0.43 – 0.72) in comparison with those within the group of cows with a BCS of ≤ 2.5 (Figure 3).

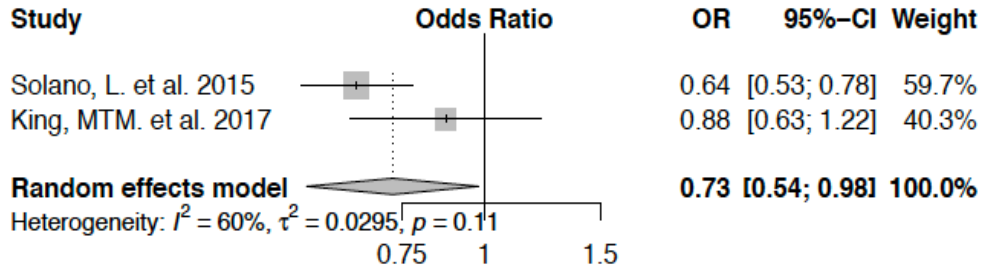

Figure 2: Forest plot for BCS 3.0 vs. BCS ≤ 2.5

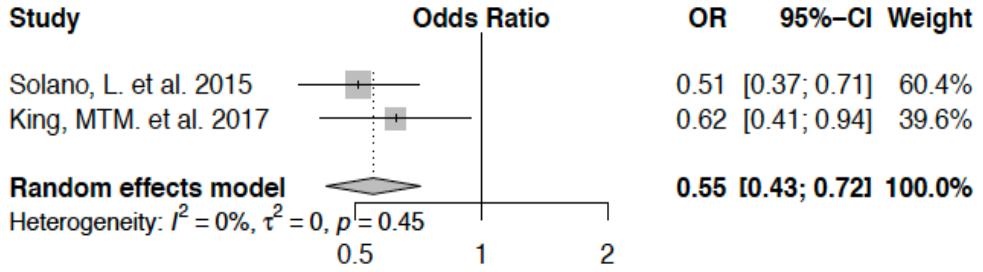

Figure 3: Forest plot for BCS ≥ 3.5 vs. BCS ≤ 2.5

The absence of claw overgrowth was the reference category and the risk for lameness in cows with overgrown claws was examined(Figure 4). Cows with overgrown claws have increased odds (OR 1.78; CI 1.50 – 2.11) of lameness compared with animals the claw of which are of normal shape.

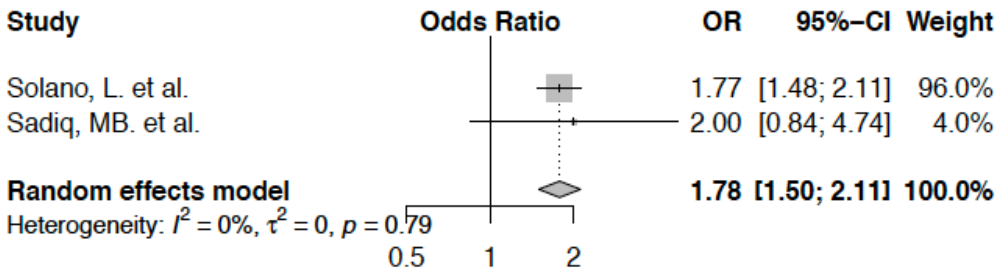

Figure 4: Forest plot for presence of claw overgrowth vs. absence of claw overgrowth

Figure 5 shows that the risk of lameness is higher (OR 2.32; CI 1.36 – 3.96) for cows during the first 120 days of milk than for animals in a later stage of lactation.

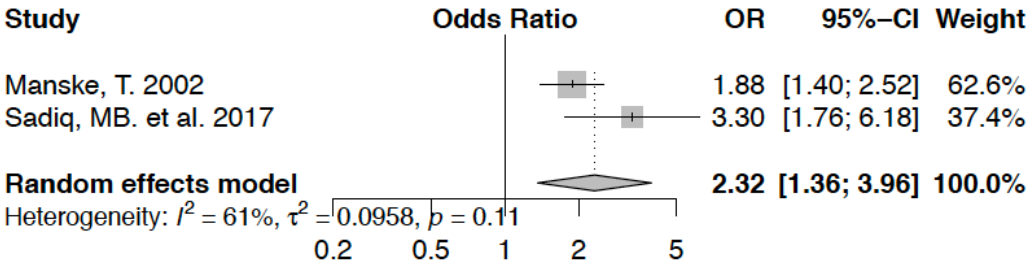

Figure 5: Forest plot for cows <120 DIM vs. animals >120 DIM

Lactating cow herd sizes of 30-50 animals or 50 or more animals, respectively, increase the odds of becoming lame (OR 1.49; CI 1.03 – 2.15 and OR 2.04; CI 1.61 – 2.58) compared with herd sizes of ≤ 29 animals (Figures 6 and 7).

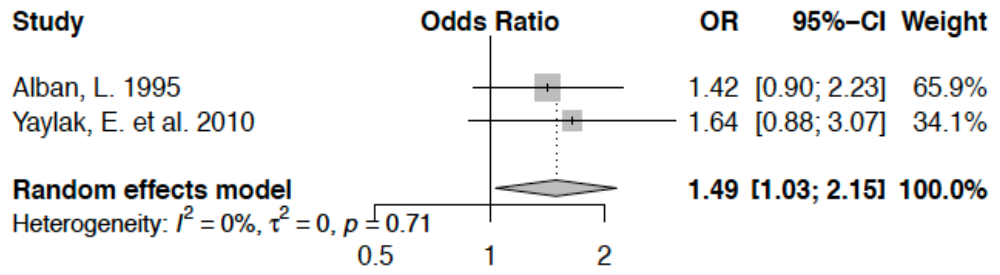

Figure 6: Forest plot for herd size of 30-50 animals vs. ≤ 29 animals

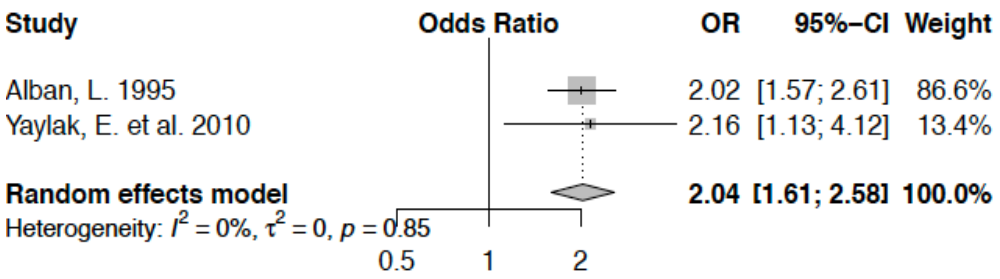

Figure 7: Forest plot for herd size of ≥50 animals vs. ≤ 29 animals

Animals in their second lactation have lower odds (OR 0.99; CI 0.62 – 1.57) of lameness in comparison with those in parity 1 (Figure 8). This is not statistically significant. Similarly, cows in their third parity have an increased yet not significant risk (OR 1.63; CI 0.77 – 3.46) for lameness (Figure 9). The risk of lameness for those animals in fourth or higher parity on the other hand is significantly higher (OR 2.46, CI 1.55 – 3.90) compared with animals in their first lactation (Figure 10).

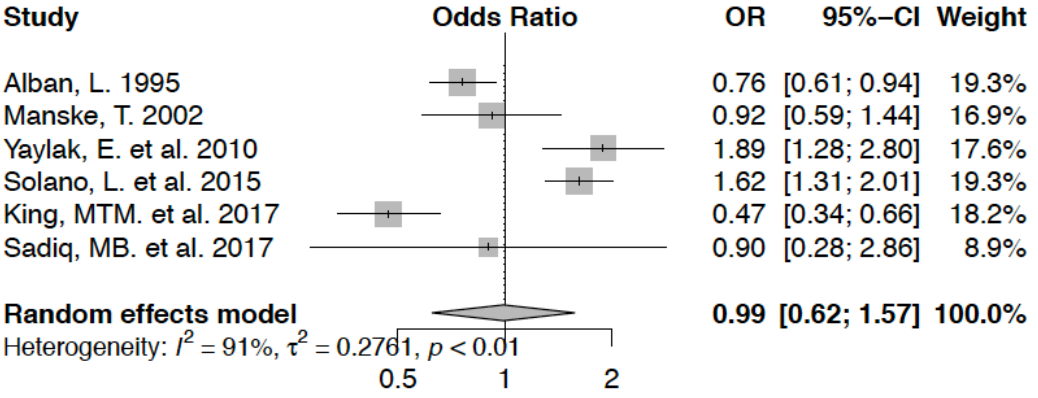

Figure 8: Forest plot for parity 2 vs. parity 1

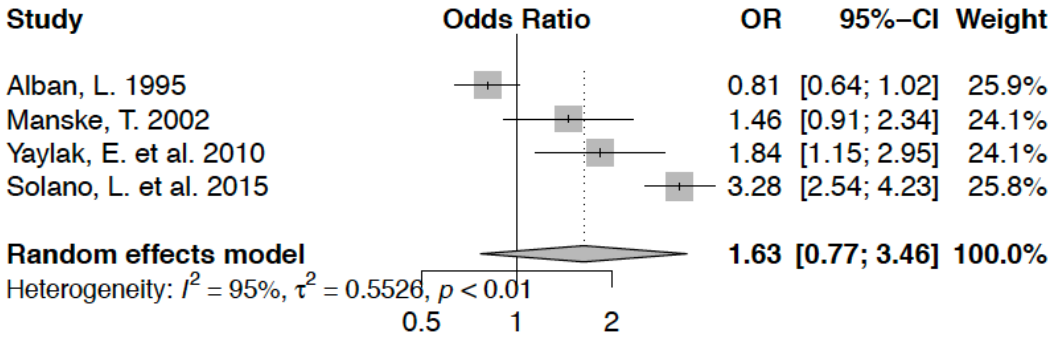

Figure 9: Forest plot for parity 3 vs. parity 1

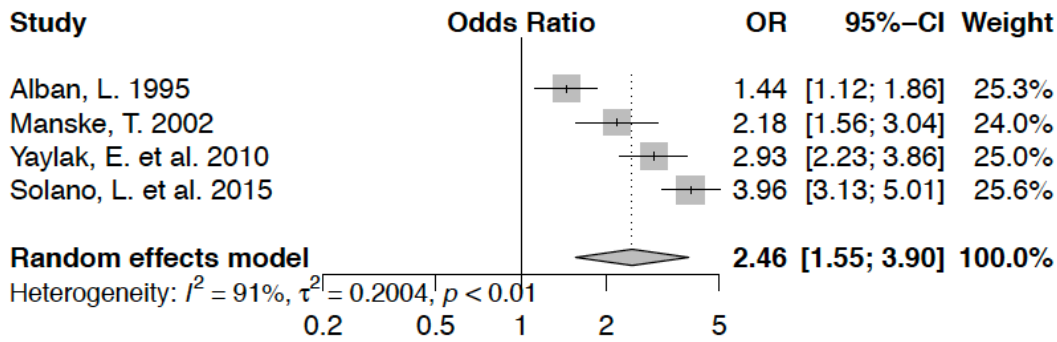

Figure 10 Forest plot for parity 4+ vs. parity 1

3. Assessment of publication bias

Funnel plots for the assessment of publication bias were created for each single meta-analysis (Figures 11-19). The graphs appeared to be mainly symmetrical and evenly distributed, although dots were not entirely located within the funnel itself. In the case of slight asymmetry, studies with larger sample sizes appeared to report outcomes closer to no effect.

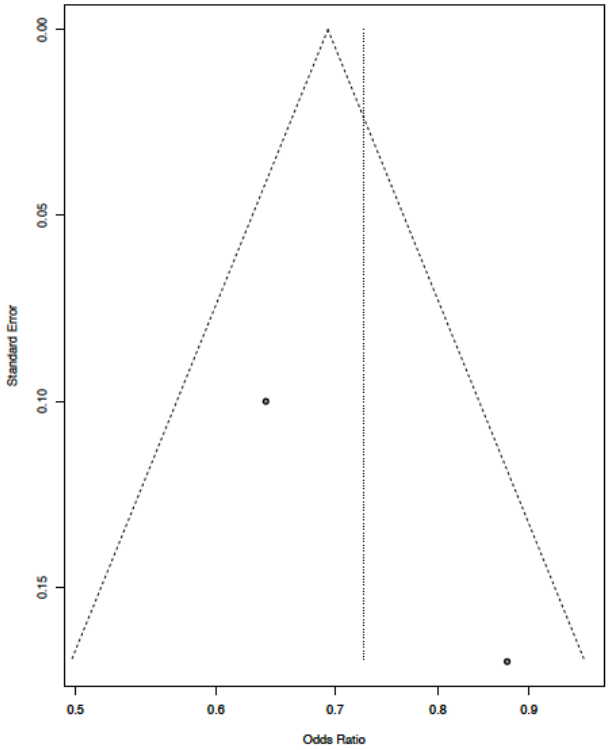

Figure 11: Funnel plot of the meta-analysis for BCS 3.0 vs BCS ≤ 2.5

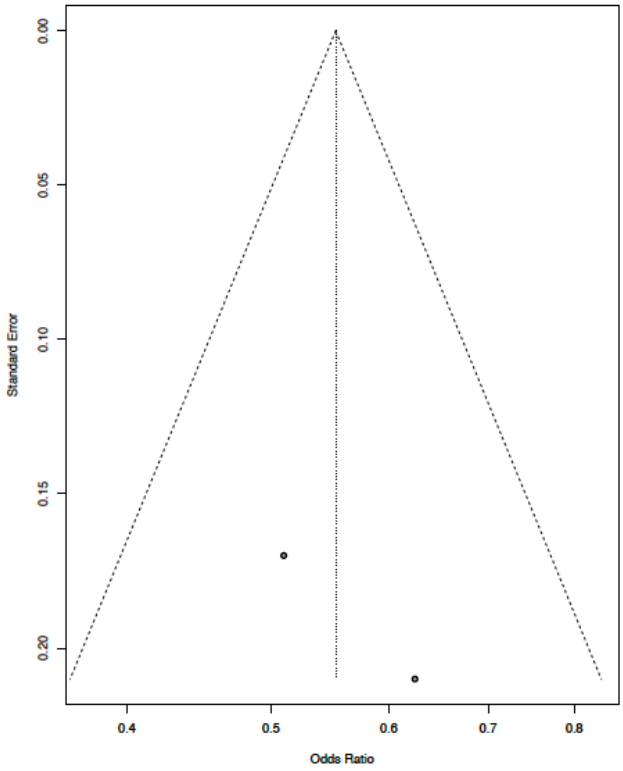

Figure 12: Funnel plot of the meta-analysis for BCS ≥ 3.5 vs BCS ≤ 2.5

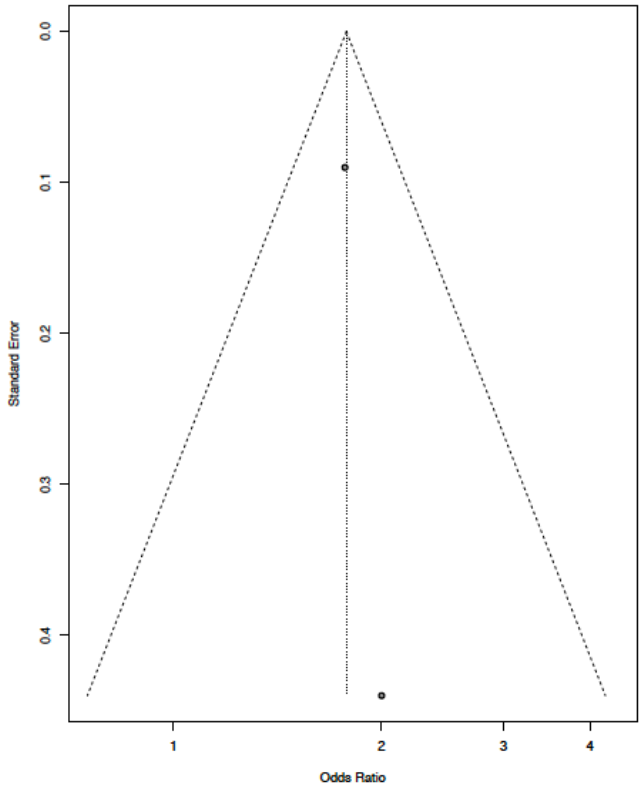

Figure 13: Funnel plot of the meta-analysis for the presence of claw overgrowth

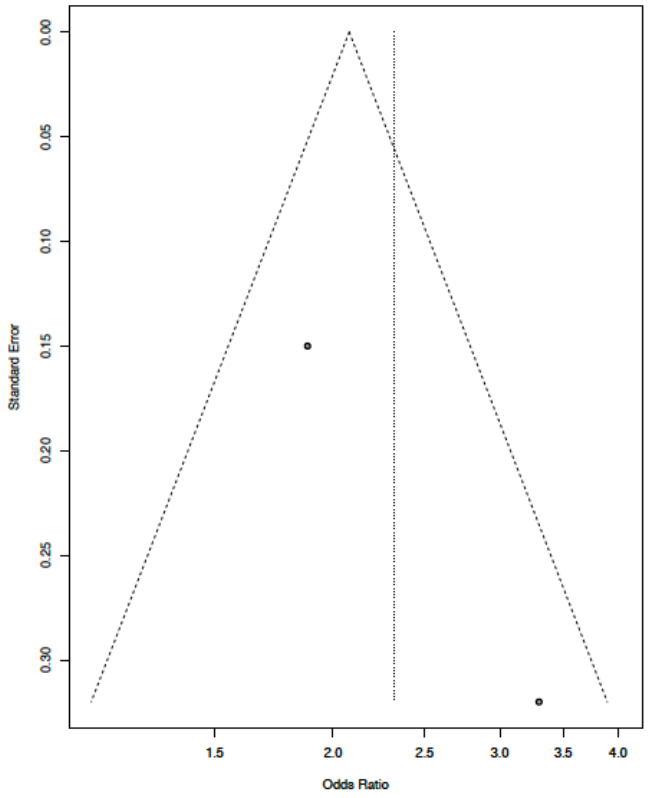

Figure 14: Funnel plot of the meta-analysis for stages of lactation (≤120 DIM vs. >120 DIM)

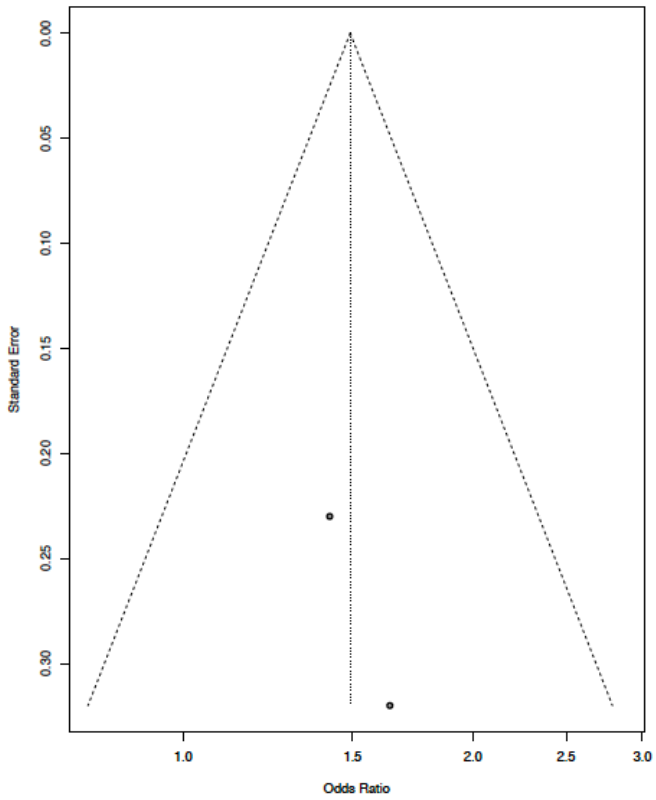

Figure 15: Funnel plot for the meta-analysis for herd size (30-50 animals vs. ≤ 29 animals)

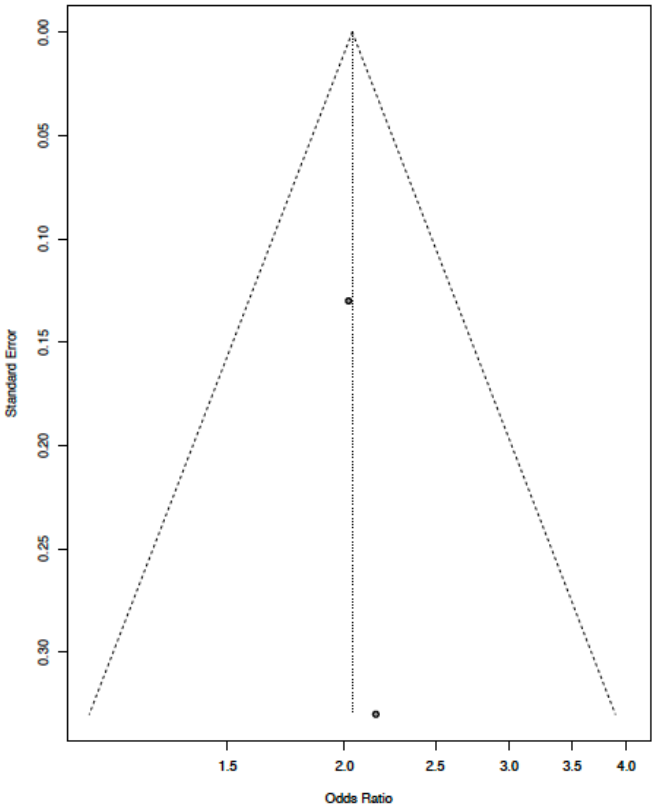

Figure 16: Funnel plot of the meta-analysis for herd size (≥50 animals vs. ≤29 animals)

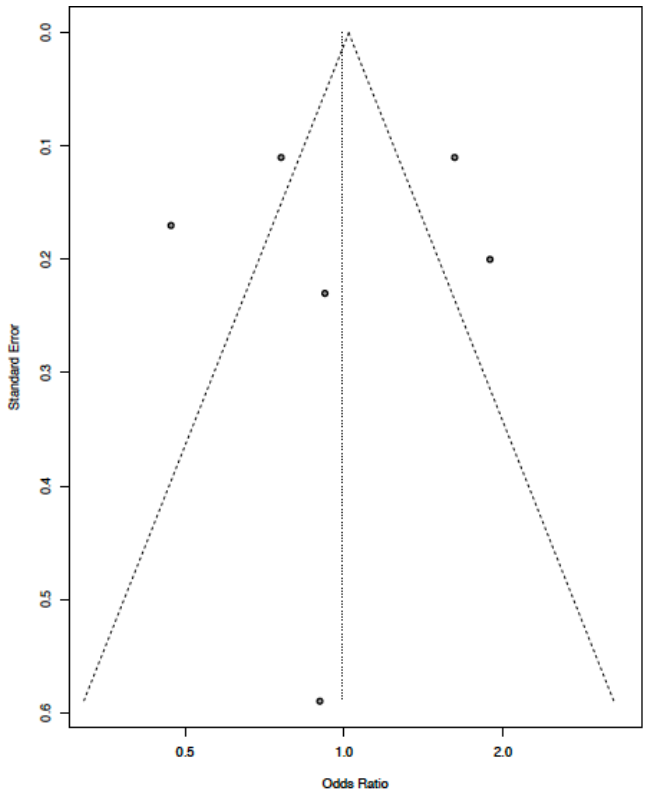

Figure 17: Funnel plot of the meta-analysis for parity (parity 2 vs. parity 1)

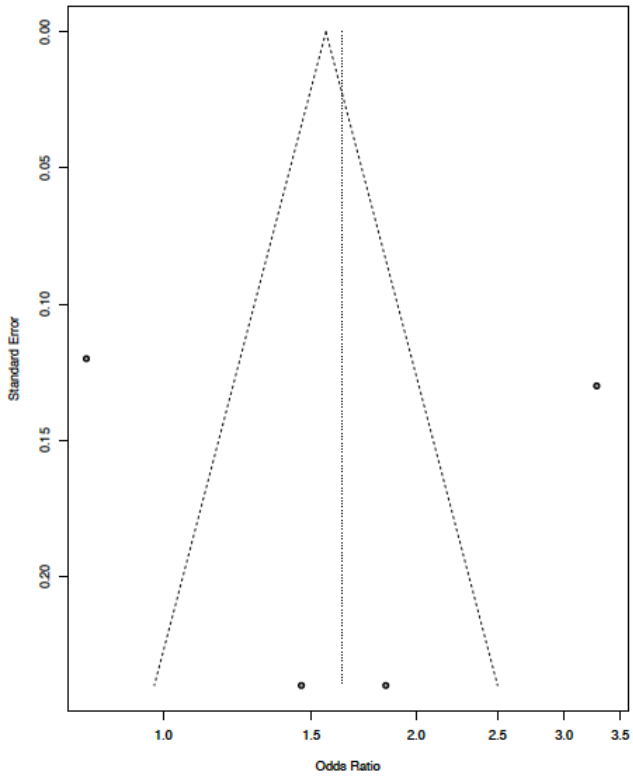

Figure 18: Funnel plot for the meta-analysis for parity (parity 3 vs. parity 1)

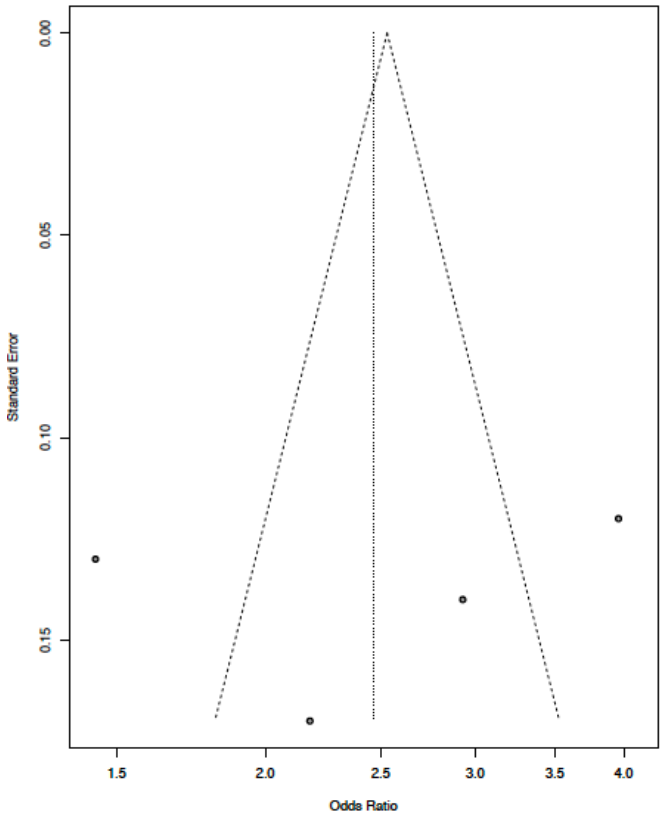

Figure 19: Funnel plot of the meta-analysis for parity (parity 4 vs. parity 1)

V. DISCUSSION

1. Discussion

1.1. General discussion of findings

The objective of this study was to give a comprehensive overview of risk factors for lameness in dairy cows on the one hand and to quantitatively synthesise information of the existing body of research on the other hand. Furthermore, it was intended to present potential areas where knowledge ought to be improved and to perform meta-analyses where possible. Out of 1941 studies retrieved initially, 128 factors that have been associated with lameness in dairy cows in the literature could be identified in a total number of 53 articles. For five different risk factors in six of these research papers, sufficient information was retrievable to perform meta-analyses to elicit their association with lameness. However, several limitations to the present analysis exist and ought to be taken into consideration when interpreting the results.

Five relevant data bases have been used for a comprehensive literature research at the beginning of the present study: MEDLINE (incl. Epub ahead of print, In process and other non-indexed citations), Web of Science, BIOSIS Previews, AGRICOLA, and VETMED RESOURCE/CABI. Initially, studies of all languages describing risk factors for lameness in dairy cows and alternative wording were admitted. This lead to a total amount of 1941 primary articles yielded in the first place.

The large number of extracted articles provides compelling evidence itself that lameness in dairy cattle has been an ongoing concern of substantial importance. In spite of the fact that literature provides an extensive amount of studies related to the issue addressed in this study, only 53 of the original 1941 studies were eligible for inclusion in the systematic review and six in meta-analyses.

Firstly, this is due to the variety of studies and the abounding plenty of risk factors research has described. Lameness in dairy cows has a multifactorial aetiology and it is hence challenging to trace its occurrence back to one factor that tips the scale. It has been exposed how single factors specifically contribute to the development and occurrence of lameness in dairy cows. In a complex system where a large

number of factors interact, it is yet difficult to quantify the specific impact of one factor on the outcome variable. Therefore, albeit the results of every single meta-analysis introduced in this research give an indication of how the presented risk factor is associated with the occurrence of lameness in dairy cows, it needs to be underscored nevertheless that they require to be interpreted in a multifactorial context.

Secondly, the small number of comparable studies included in the present work can be attributed to the fact that quantitative studies containing a full display of statistical features and detailed numbers of lame and sound animals for each risk factor are scarcely available. The latter reason led to the exclusion of studies with a lack of statistical documentation or presentation of statistically relevant quantitative information or number of animals in different groups. Regarding certain publications, it was equally necessary to calculate standard errors from confidence intervals, if only the latter were reported. This resulted in an approximation of the actual values only and may be a weakness of this study. It is inevitable to emphasise that this approach was chosen due to poor documentation and presentation of primary data in the articles that had been retrieved. The eventual outcome has not been negatively influenced by this approach, however. In general, it may be conducive from an evidence-based point to view if data were uploaded as soon as a study is published.

Thirdly, the choice of the reference category in separate risk factor studies was fairly unequal among studies and since it is necessary for meta-analyses to determine the reference category to be able to combine evidence from various studies, the Mantel-Haenszel method to pool odds ratios had to be applied. This may be understood as a weak point of the present study but again, it is due to inconsistent reporting of information in the studies we included.

A total amount of 51 studies had to be excluded, for the reason that either abstracts or full texts were not accessible and three more publications were not included due to unavailability in any of the languages that could be understood. For modern research, it is absolutely indispensable that knowledge is broadly accessible in order to be shared, understood, and taken into consideration by a wide audience. New insights into existing problems can hence be implemented and built on properly and quickly.

The present study has reinforced the perception that the majority of studies that described and evaluated risk factors for lameness in dairy cows were doing so for cows housed in free stall facilities. Lack of evidence exists specifically for cows housed in tie stall barns only. This seems unreasonable, since that husbandry method is fairly common in some regions (ZURBRIGG et al., 2005). Future research is required to gain insights into interrelationships and risk associations for lameness in dairy cattle in tie stall operations. Furthermore, even though some work has exposed that lameness prevalences tend to be higher in free stall barns compared with tie stall housings (CHAPINAL et al., 2013; FODITSCH et al., 2016; SHEARER & VAN AMSTEL, 2017; COSTA et al., 2018), the true reasons for this have not yet been discovered and may be perspectives for future investigations.

Lameness is defined as the inability to express a physiological locomotion pattern in one or more limbs most frequently as a consequence of pain (GREENOUGH, 1985; STANEK, 1997; RADOSTITS et al., 2007; BLOWEY & WEAVER, 2011). This usually presents as a reluctance to bear weight, referred to as ‘limping’, in the affected leg and abnormalities in standing and rising as well as compensatory movements of the head and the other extremities in order to mitigate pain. Further definitions of lameness have been introduced by individual research as well. Moreover, in some cases, lameness was regarded as an equivalence of the presence of certain claw-associated conditions or the fulfilment of a certain score (ALBAN, 1995; ALBAN et al., 1996; POTZSCH et al., 2003; Chapinal et al., 2013). In some cases, studies have foregone with a specific definition of lameness (FAYE & LESCOURRET, 1989). This considerable heterogeneity of nomenclature was also present in the definition of lameness among studies sifted in the course of this work.

Well-defined locomotion scoring systems have been presented in research to record characteristics and aberrations of gait in dairy cows and to quantify lameness problems in a herd. Based on the literature screened in the course of this work, 18 different approaches were displayed in the present study, which have partly been modified by several studies. This is a rather large amount of different scoring systems in relation to the number of included articles in the present research project. Whereas most studies adhered to the introduced scoring systems and the criteria for classifying a cow as lame, some studies integrated additional criteria or modified existing locomotion scoring systems. Furthermore, as for BECKER et al. (2014b)

even though they implemented a commonly used lameness scoring system (SPRECHER et al., 1997), they classified a cow as being lame with a score of ≥ 2 in sharp contrast to other studies applying the same scoring system, which have regarded a cow as lame with a score of ≥ 3 (ESPEJO et al., 2006; ESPEJO & ENDRES, 2007; WEBER et al., 2013; COOK et al., 2016; RISTEVSKI et al., 2017a). It may be problematic to appraise and compare the outcomes of different research projects if definitions and approaches vary distinctly across studies. For future investigations, following a precise and consistent nomenclature when devoting effort to the same problem is therefore recommended. This is indispensable to develop and evaluate effective interventions.

1.2. Systematic review: Methodology and limitations

Even though systematic reviews reflect the best evidence, the approach is susceptible to the introduction of bias owing to the retrospective character of the analysis and the study selection process (GREEN, 2005; GOPALAKRISHNAN & GANESHKUMAR, 2013). This is even more important to understand since the quality of systematic reviews directly derives from quality of the included studies (MOHER et al., 2009; HARRIS et al., 2013). Bias in a review can be the result of bias within the incorporated primary investigations or arise from methodological flaws or limitations. It is crucial to know that bias can enter in various forms and at all stages throughout the review process (SONG et al., 2010; WHITING et al., 2016; EKMEKCI, 2017). Therefore, minimisation and prevention of bias was attempted on several levels in the present study.

To begin with, three previously designed quality assessment tools, i.e. AMSTAR, PRISMA, and ROBIS, for the appraisal of systematic reviews have been oriented towards throughout the conduct of this study (SHEA et al., 2007; MOHER et al., 2009; WHITING et al., 2016) in order to reduce the introduction of bias to a minimum. In alignment with these tools and the recommendations given by SHAMSEER et al. (2015), a predefined protocol with a specific research question, i.e. “what are risk factors associated with lameness in dairy cows that are housed in free stall barns or tie stall facilities”, to be answered was incorporated and consecutive steps were conducted in accordance with the prespecified eligibility criteria. Subsequently, articles were collected from five different electronic data bases in an extensive literature search by a professional librarian with a proper expertise for working with electronic sources and retrieving articles in alignment

with a specific question. Hence, as many articles as possible could be extracted in the first place. Primary articles, their titles, abstracts, and full texts were searched and scrutinised for risk factors associated with lameness in dairy cows including alternative phrasing. Two reviewers independently examined titles and abstracts of all publications in compliance with the protocol. When disagreement was present in regard to the inclusion of an article, a third investigator was consulted to decide upon eligibility. The introduction of bias was further reduced by an appraisal of the reporting quality of the included primary articles by implementing a rigorous checklist developed by VON ELM et al. (2007) to strengthen the reporting of observational studies in epidemiology (STROBE). To visualise the step-by-step review process, a PRISMA flow chart was created according to MOHER et al. (2009) which incorporated detailed information on the flow of studies and the application of inclusion and exclusion criteria throughout the different phases of the present systematic review.

Studies were excluded if animals were not mainly housed in free stall or tie stall facilities. Furthermore, conference abstracts, book sections, and non-primary studies did not enter this systematic review. For the meta-analyses, only cows of the Holstein Friesian breed were incorporated within the analysis in order to ensure comparability and homogeneity. The breed question was not focused on during the systematic review process but only for the meta-analyses since the search aimed to include as many eligible studies as possible as postulated by WHITING et al. (2016). If data were not accessible from the primary article, corresponding authors were contacted to retrieve the information. Data collection was performed after an a priori consultation with an epidemiologist as well as with a biostatistician.

The ROBIS tool for the assessment of bias in systematic reviews, has placed clear emphasis upon the importance to determine areas where bias may have entered the systematic review (WHITING et al., 2016). In this context, four elements of the review process are being brought into focus: The inclusion criteria, the identification and selection of articles, the process of data collection and the appraisal of studies as well as synthesis and findings. It is therefore important to note that certain flaws may be present in the methodology of this review. The PRISMA guidelines (MOHER et al., 2009) demand an open a priori registration of systematic reviews. However, there was no possibility to register the pre-specified protocol or the a priori study design for the present study. This was due to the fact

that PROSPERO appeared be exclusive for medical studies in human patients whereas an equivalent registration institution has not been introduced in the veterinary sector. Secondly, solely observational studies could be included, which had not been determined in preparation of the present study. When specifying the research question, the PICO criteria are to be paid attention to in order to create a clearly defined question, narrowed down to a specific population, a certain intervention, comparisons and determined outcomes (WHITING et al., 2016). In the present study the sole point that may yet not have been distinctively specified a priori was "interventions", despite the fact that factors that had been associated with lameness were searched for, which may have at least partially complied with the "intervention"-criterion of PICO. It was not possible to consider the concept of PICO entirely since it had been expected that clinical trials may not be abundant in the research area this work focused on which was corroborated eventually by the fact that no clinical trials but observational studies only remained among the identified articles eventually, which confirmed the initial perception of the authors. However, in order to ensure a systematic review process, a previously specified and clearly defined agenda was followed which involved distinct information on the research topic and population of interest, i.e. risk factors associated with lameness in dairy cows housed either in free stall barns or tie stall facilities. When looking at this research question, it may appear reasonable that observational studies are more abundant addressing this area and that interventions may not be common to evaluate factors associated with the condition of lameness. Furthermore, in the context of performing meta-analyses, control cows, i.e. sound dairy cows exposed to the same factors that had been expected to be associated with the outcome, i.e. lameness, were required in the present study to calculate odds ratios.

Thirdly, even though full-text screening of studies, data extraction, and the implementation of the STROBE checklists to assess the reporting quality of primary articles were performed by one single reviewer, these procedures were discussed before starting the review process. Moreover, the second reviewer checked the decision upon inclusion after full texts had been screened in alignment with the procedures presented by WHITING et al. (2016) and an a priori discussion including a biostatistician and an epidemiologist was held in order to determine which data were to be extracted from the included studies. Finally, since the STROBE checklists provide an objectified and clearly comprehensible tool to

appraise studies, the fact that one reviewer independently assessed primary articles may only be a minor source of potential bias. If 15 out of the 22 criteria within the STROBE checklists were achieved, primary articles were included in this systematic review. The choice that 15 criteria were necessary for further inclusion was a subjective decision made by the authors since at a certain point it appeared obvious that 15 was a critical number of criteria that could be met within the primary articles. This subjective choice may be regarded as a source of bias in the present review. Given the fact that distinct definitions or consistencies are largely absent in the context of lameness in dairy cows, it may appear reasonable to accept subjectively made compromises where necessary.

1.3. Publication bias

Publication bias is a principal problem when conducting systematic reviews or meta-analyses and may interfere with the validity of results, especially since positive findings tend to be favoured for publication (JIN et al., 2014, KICINSKI et al. 2015; DALTON et al., 2016). It is therefore indispensable to address this problem appropriately. Funnel plots are the most commonly applied tool for the assessment of publication bias in systematic reviews and meta-analyses (JIN et al., 2014, COBURN & VEVEA, 2015; KICINSKI et al. 2015; CHOI et al. 2016; DALTON et al., 2016). If data are homogeneous and publication bias is not present across the assessed investigations, a funnel plot appears to be symmetrical in an inverted manner. Asymmetry or reduced density in a funnel plot may yet derive from between-study heterogeneity as well. Funnel plots were created for each single meta-analysis in order to assess the presence of potential publication bias across the primary investigations. The assessment of publication bias is yet a challenging issue which is further limited by the fact that many meta-analyses only incorporate a small amount of primary investigations and the symmetry of funnel plots may be treacherous as soon as less than 10 studies are combined in a meta-analysis (JIN et al., 2014; DALTON et al., 2016). Even though funnel plots were used for the meta-analyses in the current work, it is hence important to be cautious since the number of studies included within these analyses is small with a high of six studies in only one of the present meta-analyses. For this reason, funnel plots were not further evaluated statistically.

1.4. Meta-analyses

Evidence-based medicine uses the currently available best evidence to make clinical decisions. Furthermore, individual clinical expertise is integrated as well as external expertise in form of evidence-based research (SACKETT et al., 1996). Systematic reviews and meta-analyses reflect the best state of evidence as they synthesise large quantities of empirical data (GREEN, 2005; GOPALAKRISHNAN & GANESHKUMAR, 2013). Meta-analysis allows for the statistical integration of related studies and by obtaining a summary estimate of effect, it renders results more traceable and facilitates objective appraisal of the evidence (EGGER & SMITH, 1997; RILEY et al., 2011). This method has the potential to provide definitive answers to clinical questions, to resolve uncertainty and disagreement across studies, and to put the outcomes into the context of the currently available knowledge (COOK et al., 1997; EGGER & SMITH, 1997; BHANDARI et al., 2001; GOPALAKRISHNAN & GANESHKUMAR, 2013). Furthermore, relationships and associations between various factors can be understood and future research initiatives and guidelines may be suggested and refined. Meta-analyses are of invaluable importance if inconsistencies are present among the results of primary studies (RIED, 2006). The larger sample size within a meta-analysis enhances the power, generalisability and precision of the outcome effect estimates. However, it is imperative to understand that the quality and validity of inference drawn from each of these two aforementioned approaches conventionally relies on the quality of every single primary study they integrate (BORENSTEIN et al., 2011; CHEUNG, 2015; BELLER et al., 2018). All present meta-analyses were conducted with the assistance of a biostatistician experienced in the method as suggested by WRIGHT et al. (2007). The quantitative synthesis of comparable articles was depicted using forest plot graphs. These figures included information on the relative strength of each individual study as well as on between-study heterogeneity.

For a correct interpretation of the results of a meta-analysis, it is important to be aware of the model that has been implemented (RILEY et al., 2011). In the present study, the random effects model was chosen to display outcomes for each individual meta-analysis. Random effects meta-analyses provide the average effect across all studies within the approach and acknowledge that effects may differ across studies, whereas fixed effect analyses postulate that different studies share the same

common effect (BORENSTEIN, 2011; RILEY et al., 2011, CHEUNG, 2015). Furthermore, it takes possibly unexplained heterogeneity among studies into account. The percentage of heterogeneity in each meta-analysis, i.e. the value of I^2, or τ^2 as the variance between studies hence give an indication of the variability in effect estimates as a consequence of actual study differences rather than chance in the course of sampling (BORENSTEIN, 2011; RILEY et al., 2011, CHEUNG, 2015). Since the presence of heterogeneity in preparation of this study was expected, and because of the fact that random effects meta-analyses are mainly prominent in a medical context (RILEY et al., 2011), this approach was chosen. In order to correctly interpret the results, it is important to consider that on an individual study basis, the effect of a certain risk factor may be different from the average effect estimate yielded in the random effects meta-analysis.

Hereinafter, the five risk factors that could be integrated in meta-analyses are discussed: Body condition score, the presence of claw overgrowth, stage of lactation, i.e. days in milk, herd size, and parity.

For the meta-analysis of the association of BCS with lameness, only two studies could be included. This can be attributed to the fact that only two comparable studies that displayed data sufficiently for a meta-analysis, could be retrieved. Secondly, BCS categories and reference categories chosen to analyse the risk of cows in different body conditions for lameness, have been determined in a heterogeneous way across studies which further made it difficult to isolate combinable publications. Thirdly, no studies on the quality of association between body condition and lameness in other breeds were identified. Both studies conducted in herds of Holstein-Friesian cattle. Since Holstein-Friesian cows and other breeds common in the dairy sector such as Brown Swiss, German Simmental cattle, and Jersey all are different breeds within the same species (SAMBRAUS, 2001; BUNDESZENTRUM FÜR ERNÄHRUNG, 2018), i.e. *Bos primigenius taurus*, it is reasonable to assume that the results yielded in this meta-analysis are applicable to other breeds than Holstein-Friesians just as well. On the other hand, the lack of data on the relevance of BCS in lameness development for other breeds may provide suggestions for future investigations. It is equally reasonable to assume that BCS and lameness may be associated in a different way in other breeds than Holstein Friesian cattle, since an abundance of considerable differences and variations in physiology and body parameters has been observed in numerous dog

breeds and even within the same breed although they are members of the same species (GIESECKE et al., 1984; BODEY et al., 1998; HAY KRUAS et al., 2000; BJÖRNERFELDT et al., 2008; MEROLA et al., 2012; TORRES et al., 2014).

As for SOLANO et al. (2015) the only BCS category presented in the article, that was comparable to a BCS of 3.0 in KING et al. (2017) was 2.75-3.25, which was regarded as equivalent. Secondly, since information on the number of lame and sound animals in each BCS group was not clearly presented in the original article, the required information had to be extracted from a bar plot diagram as precisely as possible. Furthermore, a BCS of ≤ 2.5 was determined as the reference category for both studies and the values for KING et al. (2017) were calculated in order to render both studies combinable. These three procedures may be regarded as a weakness of this particular meta-analysis. Nevertheless, the results that cows with a BCS of 3.0 or ≥ 3.5 have decreased odds of lameness compared with cows with a BCS of ≤ 2.5, (OR 0.73 and 0.55, respectively) add to the evidence that a low body condition is associated with an increased risk of lameness in dairy cows as demonstrated in several studies (BICALHO et al., 2009; LIM et al., 2015; RANDALL et al., 2015; NEWSOME et al., 2017a; NEWSOME et al., 2017b; RANDALL et al., 2018). Following the 5-point scale with 0.25 increments to assess body condition in dairy cows presented by EDMONSON et al. (1989), cows with a BCS of ≤ 2.5 appear to be twice as likely to be lame compared with cows ranging in BCS from 2.75 to 3.0 (ESPEJO et al., 2006; WESTIN et al., 2016b). Non-infectious pathologies of the claw particularly appear to be initiated by means of low body condition (GREEN et al., 2014). It has been alleged that the thickness of the digital cushion is profoundly linked to body condition and decreases correspondingly to a decline in body condition (BICALHO et al., 2009). This is further conceivable due to the fact that dairy cows enter a period of reduced insulin receptor sensitivity in peripheral tissues and an increased lipolytic metabolism after parturition (COWIE et al., 1980; MCNAMARA et al., 1995; TOMLINSON et al., 2004). Hence, the digital cushion is subjected to remarkable changes and deeper structures. e.g. the corium, of the claw are hence less shielded from forces and pressure of weight-bearing (BICALHO et al., 2009; NEWSOME et al., 2017a; NEWSOME et al., 2017b) and become more susceptible to damage and lameness-causing conditions such as sole ulcers and white line disease as a consequence of disruption of claw horn growth. RANDALL et al. (2015) have therefore suggested to keep cows at a BCS of at least

2.5 for the best results in reducing lameness. Apart from that, an additional element may be the decreased feed consumption in lame cows as they are either less capable of prevailing against sound herd mates or have to modify their behaviour and spend a larger amount of time lying down (JUAREZ et al., 2003; HOEDEMAKER et al., 2009; BEER et al., 2016). The association between BCS and lameness may be part of a vicious circle and mutual causality seems rather reasonable in this context.

Claw overgrowth is positively associated with lameness in dairy cattle (DEMBELE et al., 2006; SOLANO et al., 2015) and claw trimming management hence constitutes a crucial point in managing foot health in dairy cows. It is important to consider that claw overgrowth was assessed subjectively without the implementation of an established or validated scoring system in the primary studies included in this meta-analysis. The results of our meta-analysis on the presence of claw overgrowth provide evidence to further corroborate the view that claw overgrowth increases a cow's risk of being lame (OR 1.78). It is well understood that the dorsal hoof wall shows higher rates of horn growth compared with the heel. As a result, the dorsal angle of the digit declines gradually over time (RAVEN, 1989; BLOWEY, 1998) and an increased amount of weight is put on the caudal parts of the claw. This is most pronounced in overgrown claws and may lead to bruises of the corium and the development of sole ulcers. Not only are biomechanics positively influenced by hoof trimming as weight load is more evenly distributed, but hoof growth characteristics are equally improved as horn growth is enhanced and wear attenuated (MANSON & LEAVER, 1988a, 1989). Lameness problems within a herd can therefore be effectively addressed and prevented by the implementation of correct functional claw trimming in adequately regular intervals (MANSKE, 2002; MANSKE et al., 2002; GRIFFITHS et al., 2018;FJELDAAS et al., 2006; LAVEN et al., 2008; BRUIJNIS et al., 2010; SCHULZ et al., 2016). Irrespective of the fact that several recommendations on the regularity of hoof trimming and the optimal points in time have been identified in the literature (MANSON & LEAVER, 1988; MANSKE, 2002; BLOWEY, 2005; MAXWELL et al., 2015; GRIFFITHS et al., 2018), no definitive advice can yet be given for the ideal frequency of claw trimming in dairy cows. This hence may reflect a need of future investigations to determine the most suitable trimming protocol both from an economic as well as from a physiological and animal welfare related perspective.

The meta-analysis on stage of lactation indicates that cows during the first 120 DIM

are at a remarkably higher at risk of lameness than animals after that period (OR 2.32). The initial four months after parturition challenge a cow's ability to adapt to husbandry changes and associated environmental and nutritional conditions (WHAY et al., 1997; SUNDRUM, 2015). These factors in combination with the transition from late pregnancy to the onset of lactation may facilitate the development, emergence, and deterioration of claw lesions. High milk yield in early lactation may be an important additional factor to exacerbate the situation by promoting increased loss of body mass after parturition (BICALHO et al., 2009). Digital cushion thickness decreases correspondingly and renders animals more susceptible to claw diseases, which may result in lameness. Reduction in feed consumption secondary to lameness may further aggravate these circumstances. Furthermore, the formation of horn of inferior quality may add up to the challenges that the claws are subjected to in the transition period. High milk yield requires a large quantity of nutrients for milk production itself in addition to the physiological requirements for body maintenance (LEROY et al., 2008; SUNDRUM, 2015). LEROY et al. (2008) have exposed that a high prioritisation for glucose, fatty acids, and protein from body reserves and the gastro-intestinal tract directly to the mammary gland arises in early lactation in order to guarantee the preservation of milk production. This catabolic metabolism is entailed by a decreased sensitivity to insulin in peripheral tissues (COWIE et al., 1980; TOMLINSON et al., 2004; LEROY et al., 2008). During the keratinisation process, the newly erupting horn tissue relies on the nutrient supply via diffusion from the corium (MÜLLING et al., 1999). As described above, a decreased sensitivity or concentration of insulin at the onset of lactation results in a decreased availability of nutrients in the dermal layers of the claw (HENDRY et al., 1999; MÜLLING et al., 1999; TOMLINSON et al., 2004). This is conceivable to have a negative impact on horn formation and the integrity and quality of the horn. Inferior horn that is produced during early lactation may subsequently increase the susceptibility to claw disorders and result in lameness (GREEN et al., 2002; TOMLINSON et al., 2004). Most importantly, it has been well exposed that the structure and rigidity of the digital suspensory apparatus undergo distinct changes in the transition period that culminate in a loosening of the elasticity of tissue at the dermal-epidermal lamellar junction (TARLTON et al., 2002; TARLTON & WEBSTER, 2003; KNOTT et al., 2007). Histopathological remodelling processes include compositional changes in elastin, collagen, and proteoglycans within the dermal layer likely to be induced by calving-

and lactation related changes in endocrine and metabolic pathways. Consequently, the third phalanx is rendered more mobile within the horn capsule and may add bruises and further traumatic damage to the corium in the course of decreased resilience to weight bearing which entails lameness inducing pain and the development of sole ulcers (SAMUEL et al., 1998; LISCHER, 2000; TARLTON et al., 2002; TARLTON & WEBSTER, 2003; KNOTT et al., 2007). Since 128 factors associated with lameness in dairy cows could be identified in the surveyed literature, it is reasonable to infer an intricate multifactorial aetiology in this context and in order to fully disentangle causal pathways rather than statistical associations, further research is imperative to clarify the role of certain risk factors during the dry-off period and early lactation. Understanding the pathophysiological processes that lead to lameness in dairy cows during this period is required to develop strategies to alleviate or tackle the impact of causal elements.

The current literature has presented inconsistent results regarding the association between lameness and herd size. According to several studies, a lower prevalence of lameness in larger herds reflects more professional lameness management procedures (CHAPINAL et al., 2013; CHAPINAL et al., 2014; SOLANO et al., 2015), i.e. automated production elements and additional staff for lameness detection and treatment. Similar observations have been reported by ADAMS et al. (2017). RICHERT et al. (2013) have yet not recognized a positive association between larger herd size and lameness prevalence. ALBAN (1995) hypothesised that producers may spend less time observing their animals in larger herds as a consequence of mechanisation of process steps. In larger herds, usually fewer qualified personnel per cow are available (VON KEYSERLINGK et al., 2009; SUNDRUM, 2015) and individual animals may hence be watched less intensively. Additionally, more aggressive interactions among animals may take place in larger herds and increase the risk for traumatic claw injuries and excessive standing times by lower ranking animals (BARKER, 2007). The meta-analysis on the association between herd size and lameness supports the view that larger herd size increases the odds of lameness for an individual animal (OR 1.49 and 2.04). The reasons may be as outlined previously, but it needs to be emphasised, that the present analysis was based on 2 European studies with a rather small overall herd size even in the group of large herds compared with other studies particularly from North America (SOLANO et al., 2015; ADAMS et al., 2017). Different causalities in conjunction

with differing operational structures on a farm may be present on large-scale farms in North America. For herd size, it is therefore recommended to evaluate studies from Europe and North America independently. Additionally, when assessing the impact of herd size on the risk of lameness, overstocking has to be taken into consideration as an important factor and may be the underlying true problem, since the absolute number of animals within a herd reflects a different situation than the number of cows in relation to the number of free stalls or available feeding space, respectively. An association between stocking density and lameness has been identified (KING et al., 2016). Several lines of evidence indicate that cows stand and walk excessively in overstocked pens which is detrimental to claw health and triggers the development of foot lesions (BERGSTEN, 2001; BLOWEY, 2005; ESPEJO & ENDRES, 2007; RANDALL et al., 2015; ENDRES, 2017). Prolonged times spent standing on hard surfaces interfere with a physiological blood circulation of the digital cushion which is dependent on pumping mechanisms ensured by alternating foot load when walking. Resulting anoxaemia successively impedes the integrity of horn growth or results in cessation of horn production and the formation of low quality horn. To understand the true causal agent, namely herd size or overstocking, it is important to concentrate on both variables independently in order to evaluate their significance and influence for lameness in dairy cattle.

Higher parity increases a cow's risk of becoming lame (ESPEJO et al., 2006; OIKONOMOU et al., 2013; FODITSCH et al., 2016). Multiparous cows have obviously been confronted with the confined artificial environment they are housed in for a longer time and a cumulative effect of calving associated stress, metabolic changes throughout parities and housing-related deficiencies may be detrimental to hoof conformation and claw health and add up to existing problems. Milk yield may also play an important role in this context considering that production levels usually increase as lactation number progresses (MELLADO et al., 2011). This is basically consistent with the results of our meta-analysis of the impact of parity on the risk of lameness for cows in parity 4+. Cows in parities 4 and higher have 2.46 times increased odds of being lame compared with first lactation animals. However, compared with parity 1, cows in their second and third parity have a tendency towards lower risk of lameness. Firstly, animals in their second and third lactation may be at a point in their production life where they have left behind problems of first lactation heifers. These animals usually experience substantial changes in

housing conditions after being introduced to the lactating cows group. Rearing conditions may also have been stressful and claw trimming insufficient or completely absent. Furthermore, the entire metabolism is changing in order to cope with the nutritive and energetic requirements of milk production right after calving. Additionally, due to physical inferiority, heifers rank lower in social hierarchy which may create a stressful environment for them. Secondly, animals in second and third lactation may be those animals that had been the fittest ones in first lactation. Heifers in first lactation that suffer from lameness-causing claw horn lesion are at increased risk to become lame in higher lactations (HIRST et al., 2002) and hence may have been removed from the herd already. Consequently, those animals in second and third lactation may represent a population of cows which had performed better in their first lactation with regard to claw disorders and lameness, and therefore proceeded to second lactation. Thirdly, compared to first lactation animals, it appears obvious, that cows of parity 2 and 3 have experienced functional claw trimming more frequently than heifers. The beneficial effect of correct and regular functional claw trimming has been described (MANSKE, 2002; MANSKE et al., 2002; GRIFFITHS et al., 2018). Biomechanics are enhanced, horn growth improved and the heel region, which is confronted with bearing high loads in overgrown claws, is relieved and supported in its natural function of cushioning (MANSON & LEAVER, 1988a, 1989). Moreover, cows in parity 2 and 3 may not yet have experienced the impact of cumulative detrimental effects of the artificial housing environment, high production levels and metabolic challenges as distinctively as animals in higher parities on the other hand. Considering our results, second lactation cows may hence be at a somewhat neutral point in their life regarding their risk of lameness, past the challenges of heifers on the one hand and just yet in sight of the upcoming problems of animals in higher parities on the other hand. It is however important to note that the results of the meta-analyses are not significant for parities 2 and 3. Therefore, cows in their second and third lactation may not substantially differ from first-lactation animals. To further understand the most important causes that lead to lameness specifically in second and third lactation compared to first lactation, future investigations are necessary.

An abundance of factors influence lameness in dairy cattle and yet additional light has to be shed on many interrelationships and mechanisms. Out of 128 risk factors, data could be collected and evidence was produced on the impact of five different

risk factors on lameness in dairy cows. In the course of this study, it has become increasingly apparent that despite the extensive body of research on bovine lameness and associated risk factors, only a few studies remain comparable. The interpretation of individual study outcomes may thus be challenging. Bovine lameness as a multifactorial disorder still is a major issue in the dairy sector that requires additional research in the future, preferably in a standardised way.

2. Conclusion

Lameness is a tremendous problem of the modern dairy industry. Solid evidence is needed to further tackle this issue properly, in order to improve and ensure animal welfare, longevity, and economic viability. A suitable, transparent and consistent study design is hence indispensable to interpret outcomes and to implement adequate intervention strategies. The results of the present research clearly show that considerable difficulties in accessing primary articles as well as in collecting and extracting data completely were encountered, in light of the fact that articles did not provide sufficient information and elaborate strategies had to be applied in order to receive a comprehensive selection of data to work with. Regardless of these challenges, the present study provides information on risk factors of lameness in dairy cows on the one hand and evidence on the association of five different factors with lameness on the other hand. The inference drawn from the performed meta-analyses has been put into the context of the currently available literature.

Furthermore, remarkable inconsistencies have been encountered in the definition of lameness and the approach to classify a cow as lame. Similar inconsistencies were present in regard to the definition of risk factors and the determination of reference categories of risk factors. As outlined in the previous sections, a consensus exists on the definition of lameness. However, clinicians have developed a cornucopia of different scoring systems to assess locomotion in dairy cattle. In some cases, existing scores have been further modified. In spite of the fact that most studies referred to one of the previously presented scoring systems, single studies have introduced individual measures to quantify lameness. This makes it increasingly difficult to compare studies and their outcomes. In light of the findings of the present study, it is of fundamental importance to adhere to the established approaches to assess lameness in dairy cows rather than to introduce specific

methods in individual studies. Lameness in dairy cows is too important an issue not to follow a consolidated way to quantify the problem. It would also be reasonable to clearly define factors with a risk association to lameness and to describe the optimal state in order to be able to properly appoint reference categories.

This study is supposed to aid future studies on where to place emphasis on regarding study design. A joint initiative consisting of experts in the field and epidemiologists may be an option to establish standards on consistent and well-founded study design, analysis, and reporting. This could help improving dairy cow welfare, facilitate maintaining economic efficiency, and reduce the generation of “research waste”.

VI. SUMMARY

A systematic review and meta-analyses of risk factors associated with lameness in dairy cows

Lameness in dairy cows has been an ongoing concern of great relevance to both animal welfare and productivity in modern dairy production. Affected animals are impaired in their physiological behaviour and experience pain and discomfort from the condition. Furthermore, they are likely to be prematurely removed from the herd, their milk production declines and they face a deterioration of reproductive efficiency. Approaches presented to assess locomotion and quantify lameness in dairy cows have been abundant throughout the years. Moreover, as for aetiology, many studies have examined associations between various factors related to housing circumstances, management practises, and the individual animal and the occurrence of lameness. For the purpose of a profound understanding of the development and pathophysiology of lameness in dairy cattle it is indispensable to know about the association of factors associated with housing, management and the individual animal level in order to develop effective programmes to treat lame animals and address the problem within a herd.

The objective of this systematic review was to give a comprehensive overview of risk factors for lameness in dairy cows which have been investigated in previous research. Furthermore, a synthesis of current evidence on certain risk factors was performed by means of a meta-analysis to illustrate the strength of their association with bovine lameness. Following pre-defined procedures and inclusion criteria, two observers independently included 53 articles out of a pool of 1941 articles which had been retrieved by a literature research in a first step. 128 factors that have been associated with lameness were identified in those papers. Meta-analyses were conducted for five factors presented in six different studies: Body condition score, the presence of claw overgrowth, stage of lactation, herd size, and parity.

Results indicate that a body condition score of ≤ 2.5 on a five point scale with 0.25 increments is associated with increased odds of lameness. A higher risk of being lame was also found for the presence of claw overgrowth, the first 120 days in milk, larger herd sizes, and increasing parity.

Throughout the study, profound difficulties in retrieving data and information of

sufficient quality from primary articles as well as in recovering comparable studies arose. Even though an abundance of literature on bovine lameness exists, tremendous inconsistencies and deficits are present in regard to defining and quantifying lameness, the determination of risk factors as well as statistical completeness, presentation, and reporting. To adequately address a problem of this importance to both animal welfare and economic viability, solid evidence is required in the future to develop effective intervention strategies. A consensus on how to define and record lameness and specific risk factors consistently may be an option to consider. Furthermore, knowledge and data implemented and introduced by primary studies ought to be widely accessible to be integrated in future considerations and initiatives.

VII. ZUSAMMENFASSUNG

Eine Systematische Übersichtsarbeit und Meta-Analysen zu Risikofaktoren für Lahmheit bei Milchkühen

Lahmheit bei Milchkühen stellt nach wie vor eines der Hauptprobleme in modernen Haltungssystemen dar. Die erheblichen ökonomischen Auswirkungen sowie die Beeinträchtigung der Tiere in ihrem Wohlbefinden sind weithin bekannt. Lahme Kühe sind Schmerz und Unbehagen ausgesetzt, was sich in einem beträchtlichen Einbruch in Milch- sowie Reproduktionsleistung niederschlägt. Ferner erhöht sich die Wahrscheinlichkeit, dass erkrankte Tiere vorzeitig aus dem Betrieb entfernt werden. Im Zuge der Forschung wurden über die Jahre hinweg zahlreiche Beurteilungssysteme entwickelt, um den Bewegungsablauf von Kühen zu erfassen und zu bewerten und Lahmheit zu quantifizieren. Des Weiteren hat eine Abundanz von Studien Assoziationen zwischen dem Auftreten von Lahmheit bei Milchkühen und verschiedenen Faktoren in Bezug zu Aufstallung und Betriebsführung sowie auf das Einzeltier identifiziert und evaluiert. Für das Verständnis von Pathophysiologie von Lahmheit ebenso wie für die Entwicklung geeigneter Behandlungs- und Interventionsprogramme ist eine Kenntnis von mit Lahmheit in Verbindung stehenden Faktoren der Haltung, des Managements sowie entsprechender Einzeltierfaktoren unabdingbar.

Die Zielsetzung dieser systematischen Übersichtsarbeit war es, eine umfassende Zusammenstellung der bisher in Primärstudien dargelegten, mit Lahmheit bei Milchkühen in Verbindung gebrachten Faktoren zu präsentieren. Außerdem wurden Meta-Analysen durchgeführt, um gegenwärtige Evidenz statistisch zusammenzufassen und damit die Stärke und Art der Assoziation gewisser Faktoren mit dem Auftreten von Lahmheit bei Rindern auszuführen. Nach klar definierten Arbeitsschritten wurden durch zwei Wissenschaftler 53 Studien aus einem Pool von 1941 mittels Literaturrecherche zusammengetragener Primärartikel inkludiert. In diesen 53 Veröffentlichungen konnten 128 mit Lahmheit assoziierte Faktoren ermittelt werden. Meta-Analysen konnten für fünf Faktoren aus sechs Primärstudien durchgeführt werden: Körperkondition, übermäßig gewachsene Klauen, Laktationsstadium, Herdengröße und Parität.

Die Resultate der Analyse lassen darauf schließen, dass eine Körperkondition von

≤ 2,5 auf einer Skala von 1-5 und Bewertungsschritten von 0,25 mit einem höheren Risiko für Lahmheit assoziiert ist. Ebenso konnte für die Faktoren „übermäßig lange Klauen“, „erste 120 Tage der Laktation“, „größere Herde“ sowie „höhere Parität“ ein gesteigerter Risikozusammenhang mit Lahmheit eruiert werden.

Im Rahmen der Studie offenbarten sich deutliche Schwierigkeiten, Daten und Informationen von ausreichender Qualität aus den Primärstudien zu gewinnen. Außerdem gestaltete es sich schwierig, vergleichbare Studien zu erhalten. Trotz einer Vielzahl an Studien zu Lahmheit bei Milchkühen liegen enorme Uneinheitlichkeit und Mängel speziell im Hinblick auf die Begriffsdefinition und quantitative Erfassung von Lahmheit vor. Darüber hinaus wird die Beschreibung und Festlegung von Risikofaktoren sowie die Wahl von Referenzkategorien im Rahmen statistischer Modelle sehr heterogen gehandhabt. Für die Durchführung der Meta-Analysen stellten das Fehlen von Daten und die Unvollständigkeit in der Präsentation und Wiedergabe von Informationen eine Schwierigkeit und Beeinträchtigung dar.

Um einem Problem von derartiger Gewichtigkeit für Tierwohl und Wirtschaftlichkeit angemessen entgegentreten zu können, ist es unabdingbar, sich auf die gegenwärtig beste Evidenz zu stützen, um effektive Interventionsstrategien entwickeln zu können. Für die Zukunft wäre ein konsolidierter Ansatz zur Definition und Quantifizierung von Lahmheit bei Milchkühen sowie bestimmter Risikofaktoren eine wünschenswerte Option. Außerdem sollten Daten und Ergebnisse aus Primärstudien unkompliziert zur Verfügung stehen, um in zukünftigen Überlegungen und Forschungsansätzen inkorporiert werden zu können.

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IX. APPENDIX

1. List of figures

2. List of tables

3. List of formulas

4. Study protocol (according to SHAMSEER et al., 2015)

Section 1: Administrative information

Title

Item 1a. Identification. Identify the report as a protocol of a systematic review.

Protocol for a systematic review and meta-analyses to identify risk factors associated with lameness in dairy cows housed in free stall barns and tie stall facilities.

Item 1b. Update. If the protocol is for an update of a previous systematic review, identify as such.

This is the first attempt for a systematic review in this context. No update of a previous systematic review was conducted.

Registration

Item 2. If registered, proved the name of registry (such as PROSPERO) and registration number.

Not applicable. PROSPERO is exclusive for studies in human patients according to the website. Even though the University of Nottingham has built a website for systematic reviews in the veterinary sector, an a priori registration was not possible on this website.

Authors

Item 3a. Contact information. Provide name, institutional affiliation, and email address of all protocol authors; provide physical mailing address of corresponding authors.

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Item 3b. Contributions. Describe contributions of protocol authors and identify the guarantor of the review.

AOE is the guarantor. AOE drafted the manuscript. AOE and SH contributed to the development of the selection criteria and the search strategy. SH and AR provided statistical expertise. All authors read, proved feedback, and approved the final manuscript.

Amendments

Item 4. If the report represents an amendment of a previously completed or published protocol, identify as such and indicate what changes were made; otherwise state plan for documenting important protocol amendments.

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Support

Item 5a. Sources. Indicate sources of financial or other support for the review.

There was no financial support of this study. The project was conducted in the context of a doctorate in accordance with the University of Munich. Salary was ensured to the doctoral student.

Item 5b: Sponsor. Proved the name of the review funder and/or sponsor.

Not applicable.

Item 5c Role of sponsor and/or funder. Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol.

Not applicable.

Section 2: Introduction

Rationale

Item 6. Describe the rationale for the review in the context of what is already known.

Lameness in dairy cows remains a tremendous problem in modern dairy production all over no world regardless of the fact that an abundance of studies have been conducted on this issue. The confined artificial environment dairy cows are kept in is of crucial importance in the development of lameness problems within a herd. However due to the large number of studies evaluating risk factors of lameness in dairy cows, it is challenging to handle this deluge of information. Systematic reviews have become increasingly important in medicine since they provide the possibility of an organised compilation and appraisal of large bodies of evidence. Furthermore, some may be comparable and display sufficient information to statistically integrate their findings via meta-analysis. This helps to give definite answers to clinical questions and to summarise and present evidence. Although systematic reviews have been published in the context of dairy cow lameness, e.g. prevention and treatment of digital dermatitis, no systematic review has yet been conducted to collate information on risk factors associated with lameness in dairy cows. The European Food Safety Authority has presented an insightful report on the importance of the housing environment in the development of lameness problems in dairy cows. Therefore, the objective of the present work is to give a meticulous compilation and statistical evaluation of literature by means of a systematic review and meta-analysis on risk factors for lameness in dairy cows. We aim to contribute evidence to the current knowledge by giving an intricate

exposition of literature as well as by providing a summary estimate of risk factor effects. Furthermore, areas of shortage of knowledge will be identified and outlined.

Objectives

Item 7. Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcome.

The aim of this systematic review is to identify risk factors associated with lameness in dairy cows that are housed in free stall barns and tie stall dairies.

Section 3: Methods

Eligibility criteria

Item 8. Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review.

Published studies of all type will be selected if risk factors associated with lameness in dairy cows including alternative wording are described. We expect mainly observational studies to be abundant in this context. However, to retrieve as many potentially relevant articles as possible, no certain study type (e.g. clinical trials to evaluate the influence of certain floorings or rubber mats) will be excluded. No time frame is imposed. Literature search will be performed from inception to February 27, 2018. Studies will be excluded if they are not available in Dutch, English, French, German, Italian, Portuguese or Spanish. Subsequently, studies will not be included if dairy cows are not housed in free stalls or tie stalls and if data cannot be retrieved sufficiently in order to conduct meta-analyses. Furthermore, studies need to meet the reporting characteristics suggested by the STROBE guidelines to enter this review.

Information source

Item 9. describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with

planned dates of coverage.

Literature searches will be conducted for five electronic data bases (MEDLINE (incl. Epub ahead of print, In process and other non-indexed citations), Web of Science, BIOSIS Previews, AGRICOLA, VETMED RESOURCE/CABI (https://www.cabi.org/VetMedResource/).

Search strategy

Item 10. Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated.

Both qualitative and quantitative studies will be sought. No study designs or language limits will be imposed on the search, although only studies available in Dutch, English, French, German, Italian, Portuguese or Spanish will be included due to resource limits. (MEDLINE (incl. Epub ahead of print, In process and other non-indexed citations), Web of Science, BIOSIS Previews, AGRICOLA, VETMED RESOURCE/CABI (https://www.cabi.org/VetMedResource/) will be searched. The specific search strategy will be created by a professional health sciences librarian with expertise in systematic review searching. The search strategy will be developed with input from AOE and SH. The search terms listed below will be implemented:

1. ("dairy cow" OR "dairy cows" OR "dairy farm" OR "dairy farms" OR "dairy herd" OR "dairy herds" OR "dairy cattle") AND

2. (lame* OR ((impaired OR alter* OR disturb*) AND

3. (gait OR locomotion))) AND

4. (((risk OR management OR "herd-level") AND factor*) OR prevalence OR associat*)

Study records

Item 11a. Data management. Describe the mechanism(s) that will be used to

manage records and data throughout the review.

Not applicable.

Item 11b. Selection process. State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (Screening, eligibility, and inclusion in meta-analysis).

Two authors (AOE, AS) will independently screen titles and abstracts of primary articles yielded by the search against the inclusion criteria. In case of disagreement, GKS will decide upon inclusion. Full texts will be obtained for all articles that appear to be available and in compliance with the inclusion criteria. The full texts will then be screened by AOE (and the decision checked by AS) whether these meet the inclusion criteria. Reporting quality will be assessed using the STROBE checklists. Additional information will be attempted to be obtained from primary study authors where necessary. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

Item 11c. Data collection process. Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators.

Data extraction will be performed by AOE after initial discussion with SH and AR. Data extraction will include information on author and publication date, country, risk factors for lameness in dairy cows, definition of lameness and applied locomotion scoring system, number of animals, housing system and funding of the research project. Data will be extracted and collected using using Microsoft Excel 2016 (macOS) containing information on author(s), study title, year of publication, country, group sizes i.e. absolute number or percentage of lame and sound animals with regard to different risk factors, confidence intervals, standard errors of odds ratios, and coefficients, odds ratios and p-values. Studies authors will be contacted to access data if necessary.

Data items

Item 12. List and define all variables for which data will be sought (such as PICO items, funding sources) and any pre-planned data assumptions and simplifications.

Data extraction will include information on author and publication date, country, risk factors for lameness in dairy cows, definition of lameness and applied locomotion scoring system, number of animals, housing system and funding of the research project. The latter information will be retrieved according to AMSTAR and because potentially clinical trials evaluating interventions may receive funding from the industry. Data will be extracted and collected using using Microsoft Excel 2016 (macOS) containing information on author(s), study title, year of publication, country, group sizes i.e. absolute number or percentage of lame and sound animals with regard to different risk factors, confidence intervals, standard errors of odds ratios, and coefficients, odds ratios and p-values. Studies authors will be contacted to access data if necessary. If necessary, calculations from available data will be made in order to obtain values necessary for meta-analyses.

Outcomes and prioritisation

Item 13. List and define all outcomes of which data will be sought, including prioritization of main and additional outcomes, with rationale.

The primary outcome will be dairy cows that are lame due to the occurrence of certain risk factors. However, we expect, that the definition of lameness will be very different across studies and hence be a problem Alternative wording is permitted, since we expect a large variety of nomenclature. We plan not to focus on one single definition of lameness in order to not exclude potentially relevant articles in regard to this definition.

Risk of bias individual studies

Item 14. Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis.

Graphic representation of potential bias across studies will be computed creating funnel plots via the statistical software 'R'.

Data synthesis

Item 15a. Describe criteria under which study data will be quantitatively synthesized.

If studies are sufficiently homogeneous in terms of design and comparator and if they provide enough statistical information to be used for quantitative synthesis, meta analyses will be performed using random-effects models.

Item 15b. If data are appropriate for synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ^2)

Odds ratios (OR) and their 95% confidence intervals will be calculated. Heterogeneity will be displayed in the forest plots by I^2 and τ^2).

Item 15c: Describe any proposed additional analyses (e.g. sensitivity or subgroup analyses, meta-regression).

Subgroup analyses or other additional analyses are not planned.

Meta-bias(es)

Item 16. Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies.

Graphic representation of potential bias across studies will be computed creating funnel plots via the statistical software 'R'.

Confidence and cumulative estimate

Item 17. Describe how the strength of the body of evidence will be assessed (such

as GRADE).

Reporting quality will be assessed using the STROBE guidelines.

5. Quality assessment tools for systematic reviews and meta-analyses

5.1. AMSTAR tool (SHEA et al., 2007)

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."*	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.*	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).*	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."*	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. *Note: Acceptable if not in table format as long as they are described as above.*	□ Yes □ No □ Can't answer □ Not applicable

5.2. PRISMA Statement (MOHER et al., 2009)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

6. Compliance of the publication to the present study with PRISMA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3/4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3/4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	19
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	19-21
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	19
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	20/21
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	21
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	21/22
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	22/23
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	23
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	22/23
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	22/23

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	23
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Additional file 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6/7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2 Figures 2-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Additional file 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18/19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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7. STROBE checklists (VON ELM et al., 2007)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results

8. Tables of the Appendix

Table 5: Studies included in the systematic review (n =53)

[1] doctoral thesis consisting of four individual research papers.

Author(s), Year	Study	Country	Definition of Lameness/ Locomotion Scoring System	Number of animals	Housing system
Adams et al. (2017)	Associations between housing and management practices and the prevalence of lameness, hock lesions, and thin cows on US dairy operations	USA	Score ≥ 2 on a 3-point scale (1 = sound, 2 = mildly/moderately lame, 3 =severely lame)	22,042	Free stall Tie stall
Alban (1995)	Lameness in Danish dairy cows-frequency and possible risk factors	Denmark	Contusion, foul in the foot, sole ulcer, foot rot, interdigital dermatitis, laminitis, swollen hock, arthritis, other lameness	9,762	Free stall Tie stall
Alban et al. (1996)	Lameness in tied Danish dairy cattle: The possible influence of housing systems, management, milk yield, and prior incidents of lameness	Denmark	Foul in the foot (interdigital necrobacillosis), hock lesions (tarsal cellulitis and its sequelae)	26,499	Tie stall
Andreasen and Forkman (2012)	The welfare of dairy cows is improved in relation to cleanliness and integument alterations on the hocks and lameness when sand is used as stall surface	Denmark	Score ≥ 1 on a 3-point scale (0=not lame, 1=lame, 2=severely lame)	2,573	Free stall
Battagin et al. (2013)	Genetic parameters for body condition score, locomotion, angularity, and production traits in Italian Holstein cattle	Italy	Not specified	44,218	Free stall Tie stall
Becker et al. (2014)	Lameness and foot lesions in Swiss dairy cows: II. Risk factors	Switzerland	Score ≥ 2 Sprecher et al. (1997)	1,449	Free stall Tie stall
Bernardi et al. (2009)	The stall-design paradox: Neck rails increase lameness but improve udder and stall hygiene	Canada	Not specified, scoring system by Flower and Weary (2006)	32	Free stall
Boettcher et al. (1998)	Genetic analysis of clinical lameness in dairy cattle	Canada/USA	Score ≥ 2 Wells et al. (1993a) Wells et al. (1993b)	1,342	Free stall
Bouffard et al. (2017)	Effect of following recommendations for tiestall configuration on neck and leg lesions, lameness, cleanliness, and lying time in dairy cows	Canada	Exhibition of ≥ 2 of the behaviours Leach et al. (2009), adapted by Gibbons et al. (2014)	3,436	Tie stall
Chapinal et al. (2013)	Herd-level risk factors for lameness in freestall farms in the northeastern United States and California	Canada/USA	Numerical Rating Score ≥ 3 Flower and Weary (2006), Chapinal et al. (2009)	14,112	Free stall
Chapinal et al. (2014)	Risk factors for lameness and hock injuries in Holstein herds in China	China	Numerical Rating Score ≥ 3 Flower and Weary (2006) Chapinal et al. (2009)	Not available	Free stall
Cook (2003)	Prevalence of lameness among dairy cattle in Wisconsin as a function of housing type and stall surface	USA	Score ≥ 3 on a 4-point scale 1=no gait abnormality, 2=slight lameness, 3=moderate lameness, 4=severe lameness	3,621	Free stall Tie stall
Cook et al. (2016)	Management characteristics, lameness, and body injuries of dairy cattle housed in high-performance dairy herds in Wisconsin	USA	Score ≥ 3 Sprecher et al. (1997)	9,690	Free stall
Dembele et al. (2006)	Factors contributing to the incidence and prevalence of lameness on Czech dairy farms	Czech Republic	Any degree of limping on one or more legs	Not available	Free stall
Dippel et al. (2009)	Risk factors for lameness in cubicle housed Austrian Simmental dairy cows	Austria/ Germany	Score ≥ 3 Winckler and Willen (2001)	832	Free stall
Dippel et al. (2009)	Risk factors for lameness in freestall-housed dairy cows across two breeds, farming systems, and countries	Austria/ Germany	Score ≥ 3 Winckler and Willen (2001)	3,514	Free stall
Espejo et al. (2006)	Prevalence of lameness in high-producing Holstein cows housed in freestall barns in Minnesota	USA	Score ≥ 3 Sprecher et al. (1997)	5,626	Free stall

Table 5 (continued): Studies included in the systematic review (n=53)

Espejo and Endres (2007)	Herd-level risk factors for lameness in high-producing Holstein cows housed in freestall barns	USA	Score ≥ 3 Sprecher et al. (1997)	5,626	Free stall
Faye and Lescourret (1989)	Environmental factors associated with lameness in dairy cattle	France	Not specified	1,712	Free stall Tie stall
Foditsch et al. (2016)	Lameness Prevalence and Risk Factors in Large Dairy Farms in Upstate New York. Model Development for the Prediction of Claw Horn Disruption Lesions	USA	Visual locomotion score ≥ 2 Bicalho et al. (2007a)	7,687	Free stall
Frankena et al. (2009)	The effect of digital lesions and floor type on locomotion score in Dutch dairy cows	Netherlands	Score ≥ 3 Manson and Leaver (1988)	225	Free stall
Green et al. (2010)	Associations between lesion-specific lameness and the milk yield of 1,635 dairy cows from seven herds in the Xth region of Chile and implications for management of lame dairy cows worldwide	Chile	Foot lesions causing lameness, diagnosed and recorded by farmers	1,635	Free stall
Green et al. (2014)	Temporal associations between low body condition, lameness and milk yield in a UK dairy herd	UK	Identifiable impaired mobility	1,.137	Free stall
Groehn et al. (1992)	Risk factors associated with lameness in lactating dairy cattle in Michigan	USA	any abnormality in locomotion as determined by producer or farm veterinarian or both	3,610	Free stall Tie stall
Gudaj (2012)	Associations between the occurrence of lameness, number of orthopaedic blocks used by hoof trimmers and management risk factors in dairy cow herds	Hungary	Score ≥ 3 Sprecher et al. (1997)	11,422	Free stall
Hedges et al. (2001)	A Longitudinal Field Trial of the Effect of Biotin on Lameness in Dairy Cows	UK	Not specified	900	Free stall
Hettich et al. (2007)	Factors associated to lameness in 50 dairy herds in the X-th Region, Chile	Chile	Sprecher et al. (1997), modified by Tadich et al. (2005)	7,501	Free stall
Hirst et al. (2002)	A mixed-effects time-to-event analysis of the relationship between first-lactation lameness and subsequent lameness in dairy cows in the UK	UK	Not specified	611	Free stall
Hultgren (2007)	Alley-floor design, claw lesions and locomotion in Swedish loose-housed dairy cattle	Sweden	Score ≥ 1 Sprecher et al. (1997), modified	183	Free stall
King et al. (2017)	Cow-level associations of lameness, behavior, and milk yield of cows milked in automated systems	Canada	Score ≥ 3 Flower and Weary (2006)	1,218	Free stall
King et al. (2016)	Associations of herd-level housing, management, and lameness prevalence with productivity and cow behavior in herds with automated milking systems	Canada	Score ≥ 3 Flower and Weary (2006)	1,230	Free stall
Manske (2002)[1]	Hoof lesions and lameness in Swedish dairy cattle: prevalence, risk factors, effects of claw trimming, and consequences for productivity	Sweden	Partly specified Score ≥1 on a 3-point scale (0=sound, 1=mild variation from normal gait, 2=clearly favouring one or more limbs, 3=extremely unwilling to put weight on one or more limbs or recumbent	4,899/ 3,444/ 2368[1]	Free stall Tie stall
Morabito et al. (2017)	Effects of changing freestall area on lameness, lying time, and leg injuries on dairy farms in Alberta, Canada	Canada	Presence of limp Solano et al. (2015) Vasseur et al. (2015)	839	Free stall
Newsome et al. (2017)	A prospective cohort study of digital cushion and corium thickness. Part 2: Does thinning of the digital cushion and corium lead to lameness and claw horn disruption lesions	UK	Score ≥ 2 Thomas et al. (2015)	179	Free stall

Table 5 (continued): Studies included in the systematic review (n=53)

O'Driscoll et al. (2009)	The effect of floor surface on dairy cow immune function and locomotion score	Ireland	Not specified, scoring system by O'Callaghan et al. (2003), modified	27	Free stall
Oikonomou et al. (2011)	Effect of polymorphisms at the STAT5A and FGF2 gene loci on reproduction, milk yield and lameness of Holstein cows	Greece	Not specified, scoring system by Sprecher et al. (1997)		Free stall
Onyiro et al. (2008)	Risk factors and milk yield losses associated with lameness in Holstein-Friesian dairy cattle	Scotland	Not specified, scoring system by Manson and Leaver (1988)	248	Free stall
Perez-Cabal and Alenda (2014)	Clinical lameness and risk factors in a Spanish Holstein population	Spain	Gait abnormality	3,459	Free stall
Potzsch et al. (2003)	The impact of parity and duration of biotin supplementation on white line disease lameness in dairy cattle	UK	white line lameness, when examining veterinarian considered that a white line disease was the cause of lameness	900	Free stall
Ristevski et al. (2017)	Influence of body condition score and ultrasound-determined thickness of body Fat deposit in Holstein-Friesian cows on the risk of lameness developing	Croatia/ Macedonia/ Serbia	Score ≥ 3 Sprecher et al. (1997)	100	Free stall
Ristevski et al. (2017)	Milk production, body condition score and metabolic parameters at the peak of lactation as risk factors for chronic lameness in dairy cows	Croatia/ Macedonia/ Serbia/ Slovenia	Score ≥ 3 Sprecher et al. (1997)	100	Free stall
Rouha-Mulleder et al. (2009)	Relative importance of factors influencing the prevalence of lameness in Austrian cubicle loose-housed dairy cows	Austria	Not specified, scoring system by Winckler and Willen (2001)	2,360	Free stall
Sadiq et al. (2017)	Prevalence of lameness, claw lesions, and associated risk factors in dairy farms in Selangor, Malaysia	Malaysia	Score ≥ 3 DairyCo (2007)	251	Free stall
Sarjokari et al. (2013)	Prevalence and risk factors for lameness in insulated free stall barns in Finland	Finland	Score ≥ 3 Sprecher et al. (1997), modified	3,459	Free stall
Sogstad et al. (2005)	Lameness and claw lesions of the Norwegian red dairy cattle housed in free stalls in relation to environment, parity and stage of lactation	Norway	Not specified	1,540	Free stall
Solano et al. (2015)	Prevalence of lameness and associated risk factors in Canadian Holstein-Friesian cows housed in freestall barns	Canada	Score ≥ 3 Flower and Weary (2006)	4981	Free stall
Weber et al. (2013)	Genetic parameters for lameness and claw and leg diseases in dairy cows	Germany	Score ≥ 3 Sprecher et al. (1997)	326	Free stall
Wells et al. (1993)	Individual cow risk factors for clinical lameness in lactating dairy cows	USA	Score ≥ 2 on a 5-point scale (0=none, 1=mild, 2=moderate, 3=severe, 4=non-ambulatory)	1,654	Free stall
Wells et al. (1995)	Effect of long-term administration of a prolonged release formulation of bovine somatotropin (Sometribove) on clinical lameness in dairy-cows	USA	Score ≥ 2 on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe)	188	Free stall
Wells et al. (1995)	Some risk factors associated with clinical lameness in dairy herds in Minnesota and Wisconsin	USA	Score ≥ 2 on a 5-point scale (0=none, 1=mild, 2=moderate, 3=severe, 4=non-ambulatory)	Not available	Free stall Tie stall
Westin et al. (2016)	Cow- and farm-level risk factors for lameness on dairy farms with automated milking systems	Canada	Presence of obvious limp Flower and Weary (2006)	1,378	Free stall
Wongsanit (2015)	Prevalence and risk factors for lameness in dairy cows raised in small holder farms in western Thailand	Thailand	Score ≥ 3 Sprecher et al. (1997)	1,151	Free stall Tie stall
Yaylak et al. (2010)	The effects of several cow and herd level factors on lameness in Holstein cows reared in Izmir Province of Turkey	Turkey	Score ≥ 3 Sprecher et al. (1997)	1,078	Free stall

X. ACKNOWLEDGEMENTS

„In jede hohe Freude mischt sich eine Empfindung der Dankbarkeit“

(Marie Freifrau von Ebner-Eschenbach, *Aphorismen*, 1911)

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