Risk factors for race-associated sudden death in Thoroughbred racehorses in the UK (2000-2007)

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Summary

Reasons for performing study: Sudden death adversely affects racehorse welfare, jockey safety and the public perception of horseracing.

Objective: To describe the risk of racing-associated sudden death in Thoroughbred racehorses in the UK from 2000-2007, to identify if there were risk factors uniquely associated with sudden death and to improve the understanding of the pathogenesis of racing-associated sudden death by identification of risk factors for such cases.

Methods: A sudden death was defined as an acute collapse and death, in an apparently healthy Thoroughbred racehorse, during or immediately after racing, in the absence of clinical data indicative of a catastrophic orthopaedic injury. The retrospective study included 201 case starts and 705,712 control starts. Univariable and multivariable logistic regression were used to identify risk factors for sudden death at any one start.

Results: In the multivariable model, age, distance, race type, season and number of starts in the 60 days prior to the race were associated with sudden death.

Conclusions: The risk factors identified in this study are not uniquely associated with sudden death and have been also been identified in studies using all causes of fatality as the outcome. These data suggest that a generic approach to reduce fatal musculoskeletal injury and sudden death may be possible.

Relevance: The identification of risk factors allows speculation on the underlying mechanisms of sudden death in racing. This may stimulate hypothesis-led investigations into the pathogenesis of exercise-related arrhythmias, EIPH and blood vessel rupture.

Introduction

Sudden death associated with exercise in the apparently healthy Thoroughbred racehorse appears to be a rare occurrence; however, the risk of such events has only been quantified in racehorses in Victoria, Australia (Boden *et al.* 2006). The risk of sudden death in that population was 0.08 per 1000 starts in flat races and 0.29 per 1000 starts in jump races, and the proportion of racing fatalities which were classified as sudden death (proportional mortality rate of sudden death) was 19% in flat races and 3.5% in jump races. In other

Thoroughbred populations where proportional mortality rates have been recorded, similar proportions of racing fatalities were attributed to sudden death: 12% (256/1981) in the UK (2000-2009) (data supplied by the British Horseracing Authority, reproduced with permission) and 9% (58/659) in California, USA (Johnson 1994a).

Risk factors for catastrophic musculoskeletal injury associated with racing have been investigated (Cohen *et al.* 2000; Cohen *et al.* 1997; Estberg *et al.* 1995; Estberg *et al.* 1998a; Estberg *et al.* 1996b; Estberg *et al.* 1998b; Hernandez *et al.* 2001; Hernandez *et al.* 2005; Kane *et al.* 1998; Kane *et al.* 1996; Parkin *et al.* 2004a, b, 2005b, 2006; Peloso *et al.* 1994). Other risk factor studies have used fatality as an outcome (Boden *et al.* 2007a, b; Henley *et al.* 2006; Williams *et al.* 2001) and have therefore included catastrophic musculoskeletal injuries as well as sudden death cases. These studies using fatality as an outcome have identified associations between fatality and age, gender, prior racing history, race length, racecourse location, surface conditions, race type, running the first race of a new type, season and year (Boden *et al.* 2007a, b; Henley *et al.* 2006; Williams *et al.* 2001). However there are no published studies investigating risk factors for racing-associated sudden death alone. This is probably due to the rarity of sudden death and the difficulty in clarifying case definition without post mortem examination. In most racing jurisdictions post mortem examination is not routinely done due to logistical difficulties and expense.

The aims of this study were to describe the risk of sudden death in the UK, to identify if there were factors uniquely associated with sudden death and to improve the

understanding of the pathogenesis of racing-related sudden death through the identification of risk factors. A sudden death was defined as an acute collapse and death, in an apparently healthy Thoroughbred racehorse, during or immediately after racing, in the absence of clinical data indicative of a catastrophic orthopaedic injury.

Materials and methods

Potential risk factors for sudden death in flat or jump races in the UK from 1/1/2000-31/12/2007 were investigated using a retrospective case-control study with 201 case starts and 705,712 control starts. The study was conducted at the level of the start (where a start represented a horse starting the race).

Selection of cases and controls

This study was specifically designed as a whole population study to make use of systematically collected data from all starts in the given study period. Data on all racing starts from 01/01/2000 – 31/12/2007 inclusive were obtained from the Equine Science and Welfare (ESW) database compiled by the British Horseracing Authority (BHA).

A case start was defined as a start in a race that resulted in sudden death. A sudden death was defined as an acute collapse and death, in an apparently healthy Thoroughbred racehorse, during or immediately after racing, in the absence of clinical data indicative of catastrophic orthopaedic injury.

Three cases classified as sudden death by the racecourse veterinarians were removed from the database as they occurred before the start. All non-case starts in the database were used as control starts except one start where data were incomplete. A control start could therefore be a case horse in a start prior to its death or a start for a non-case horse. This resulted in 3,511 controls per case start.

Risk factors

A total of 25 variables for each start were used in the analysis. These variables comprised four horse-related variables (age, animal type, use of eye equipment and use of a tongue-tie), seven prior racing history-related variables (starts ever, starts in the last 30 days, starts in the last 60 days, starts in the last 90 days, starts in the last 180 days, starts in the last 365 days and total money won), two jockey and handicap-related variables (weight-carried and type of handicap), ten race-related variables (distance, change in run distance, race class, race time, race type, number of runners, running sequence, season, selling/claiming and the value of the race) and two track-related variables (surface and going).

Details of the 705,913 starts and potential explanatory variables were downloaded into an Access database (Microsoft Access 2003[1]).

Statistical power

The power calculation indicated that the study will provide at least 80% power to detect odds ratios of 1.7 or more, with 95% confidence, given exposure prevalence in the control population of between 0.13 and 0.73.

Descriptive Statistics

Descriptive statistics (mean, median, minimum and maximum) were generated for each continuous variable (Boden *et al.* 2007a). The "best fit" of the variable was determined by graphical assessment of the relationship between the log odds of the outcome by categories of independent variable (Boden *et al.* 2007a). If the relationship was non-linear, binary or polytomous categorical terms were investigated at the univariable level and multivariable level (Parkin *et al.* 2005a).

Model Building

Potential risk factors were screened using univariable logistic regression. Variables with a likelihood ratio test P value ≤ 0.25 were available for inclusion in subsequent single level, multivariable logistic regression model building.

A causal web diagram (supplementary information) was also developed based on biologically plausible hypotheses. The multivariable model was created using a manual method based on the causal web. Variables were retained in the multivariable model if

the likelihood ratio test P-values were <0.05 when establishing the model. The Wald test P-value was used when comparing categories with the reference category. The multivariable model therefore identified the effects of the retained variables having controlled for the effects of other significant variables within the model. Biologically plausible interactions between variables in the final model were identified and interaction terms were generated and assessed (Boden *et al.* 2007a). All starts were investigated for clustering within horse, jockey, trainer, course and sire (data on case dam were not available). Intra-class correlation coefficients (ICCs), variance inflation factors (VIFs) and rhos were calculated for each of these levels.

Fit of the model and regression diagnostics

The fit of the final single-level multivariable model was assessed using the Hosmer-Lemeshow goodness-of-fit test (Hosmer and Lemeshow 2000). Regression diagnostics were performed and covariate patterns with the greatest Pearson residual, standardised Pearson residual, leverage, delta beta, delta χ^2 and delta deviance values were identified. Individual observations within these covariate patterns were then removed from the model and changes in the direction and value of the coefficients were examined (Dohoo *et al.* 2003; Hosmer and Lemeshow 2000). The predictive ability of the model was determined by generating a receiver operating characteristic (ROC) curve.

Statistical Analysis

StataSE 10.0[2] was used to perform all statistical analyses.

Results

A total of 705,913 starts were represented in the study population with 201 case starts and 705,712 control starts. Sudden death occurred during the race in 114 of the case starts, and immediately after the race in 70 of the case starts. The timing of the sudden death was not specified in the other 17 cases.

The overall risk of sudden death was 0.3 per 1000 starts (201/705,913). The risk of sudden death in the different races types was 0.07 per 1000 starts (22/319,872) in turf flat races, 0.09 per 1000 starts (12/128,699) in all-weather track (AWT) flat races, 0.4 per 1000 starts (9/21,518) in National Hunt flat (NH flat) races, 0.5 per 1000 starts (71/146,543) in hurdle races and 1 per 1000 starts (87/89,281) in steeplechases.

Univariable Analysis

Descriptive statistics for the continuous variables entered into the final model are presented in Table 1. Univariable analysis for all the variables entered into the model building process is presented in Table 2. A total of 15 variables of the 25 variables screened at univariable level were used in the building of the final multivariable model.

Univariable analysis of variables that were not entered into the model building process is presented as supplementary information online (Table 4).

Multivariable Analysis

The final multivariable model is shown in Table 3. This model represents the effects of the retained variables having controlled for other significant variables identified in the univariable analysis. Sudden death was associated with age, distance of race, type of race, season and the number of starts in the 60 days prior to the race. Increasing age was associated with increased odds of sudden death (OR per extra year 1.3, 95% CI 1.2-1.4). Increasing distance was associated with increased odds of sudden death (OR per extra km 1.3, 95% CI 1.1-1.6). Increasing number of starts in the last 60 days was associated with reduced odds of sudden death (OR per extra start 0.8, 95% CI 0.7-0.9). Compared with racing on the flat, sudden death was more likely to occur in starts in hurdle races (OR 2.2, 95% CI 1.2-4.0), steeplechase races (OR 2.3, 95% CI 1.1-4.6) and NH flat races (OR 3.1, 95% CI 1.4-7.1). Racing in the summer was associated with increased odds of sudden death when compared to racing in spring, winter or autumn (OR 1.8, 95% CI 1.3-2.5).

None of the interaction terms were statistically significant. Although there was no evidence of clustering when assessing rho or the intraclass correlation coefficients (ICCs), the variance inflation factors (VIFs) for course, horse, jockey, sire and trainer were greater than 1. However, the large VIFs were driven by the large number of observations per level (as the ICC values were small). To investigate this further, the

model was fitted with course, horse, jockey, sire and trainer as random effects. There was no significant change in coefficients, standard errors or odds ratios so the fixed effects model was retained.

Removal of covariate patterns with the greatest Pearson residual, standardised Pearson residual, leverage, delta beta, delta χ^2 and delta deviance values did not alter the direction of any of the odds ratios. No particular covariate patterns were considered to be influential.

There was no evidence of lack of fit for the model (H-L statistic 0.93, p-value 0.82). The area under the ROC curve was 0.81.

Discussion

This is the first study to investigate risk factors for racing-related sudden death alone. In the final model one horse-level variable (age), one prior racing history-related variable (starts in the 60 days prior to the race) and three race-level variables (distance, type and season) were associated with sudden death.

The area under the ROC curve was 0.81. A model with an area under the ROC curve of greater than 0.8 is considered to provide excellent discrimination between cases and controls (Hosmer and Lemeshow 2000). However due to the extremely low incidence of sudden death the positive predictive value of the model is very low and as such the model

should not be regarded as a predictive model. Rather it is intended to help generate hypotheses regarding the pathogenesis of sudden death in race horses.

The model produced in this study represents the effects of the retained variables having controlled for other variables that were significant at univariable level. For example the odds of sudden death associated with a steeplechase race are reduced from 12.87 in the univariable analysis to 2.26 in the multivariable analysis. This reflects confounding by other variables such as distance (steeplechase races are longer than other race types) but shows that even once distance is controlled for there is an increased risk of sudden death in a steeplechase race. The precise mechanisms by which these retained variables contribute to death are unclear and the following discussion provides a speculative rather then proven explanation for the findings. It is hoped that this speculation may lead to development of hypothesis-led studies to further our understanding of the mechanisms of sudden death on UK racecourses.

There are no large published post mortem studies of sudden death cases in the UK and post mortem data were not available for horses in this study. In other racing populations around the world the following two conditions have been identified as the major definitive causes of sudden death: pulmonary haemorrhage(19-82% of cases) (Brown *et al.* 1988; Gunson *et al.* 1988; Johnson 1994a; Lyle *et al.* 2011) and idiopathic blood vessel rupture (9-24% of cases) (Gelberg *et al.* 1985; Lyle *et al.* 2011; Platt 1982). (It is important to note that pulmonary haemorrhage is commonly identified during post mortem examination of sudden death cases but death is only attributed to this finding in

some cases (Lyle *et al.* 2011).) Importantly though, the cause of death often remains unknown in a significant number of cases (20-68%) despite thorough post mortem examination(Brown *et al.* 1988; Gelberg *et al.* 1985; Johnson 1994a; Lyle *et al.* 2011; Platt 1982; Vaughan and Mason 1976). The most likely explanation for cases in which a definitive diagnosis is not reached is a fatal cardiac arrhythmia although this remains unproven. Assuming similar pathology in cases of sudden death in the UK from 2000-2007 compared to racing populations in these previous post mortem studies, the risk factors identified in this study are likely risk factors for cases with negative post mortem findings (likely fatal cardiac arrhythmia) or cases in which death is attributed to pulmonary haemorrhage or vascular rupture.

Distance

The odds of sudden death increased 1.3-fold with every 1km increase in race length. In this study 35% (70/201) of sudden deaths occurred after the race and in a previous study 43% (114/268) of sudden deaths occurred in the post-exercise period (Lyle *et al.* 2011). In addition, preliminary data from another study involving observation of race videos reveals that sudden deaths that occur during races occur towards the end of the race (C.H.Lyle, *unpublished observation*). These observations illustrate that most sudden deaths occur after completing or almost completing the full race distance. Increased exposure time at risk during longer races may therefore contribute to this finding.

Inconsistent with exercise-induced pulmonary haemorrhage (EIPH) as a cause of death is that epistaxis/EIPH have been more commonly identified after shorter races (<1400-

1600m) than longer races (Hinchcliff *et al.* 2010; Takahashi *et al.* 2001). However it should be noted that investigations of EIPH have had variable study design with some studies using the presence of epistaxis as a diagnosis of EIPH while other studies have used tracheobronchoscopy for diagnosis of EIPH and this will have affected the results of these studies. In discussing these studies we have used the term "epistaxis" if the diagnosis of EIPH was made on the observation of epistaxis and the term "EIPH" if the diagnosis of EIPH was made using tracheobronschoscopy.

Increased race length may cause more severe metabolic derangements which may contribute to the development of fatal ventricular arrhythmias. Exercise-related arrhythmias are poorly understood in horses but ventricular premature complexes (VPCs) are commonly identified immediately post-exercise in apparently healthy horses (Physick-Sheard and McGurrin 2010; Ryan *et al.* 2005). Such VPCs could initiate fatal ventricular fibrillation and the immediate post-exercise period is well recognised as a risk period of sudden death in people (Paterson 1996). During intense exercise in horses there is a decrease in blood pH, increase in plasma potassium (Harris and Snow 1992) and increase in circulating catecholamines (Snow *et al.* 1992). If any of these metabolic derangements were to occur alone there would be an increased risk of fatal cardiac arrhythmia (Paterson 1996). However, these metabolic changes are well tolerated during exercise as the combination of these metabolic derangements results in mutual antagonism; the catecholamines offset the harmful effects of acidosis and hyperkalaemia and vice versa (Paterson 1996). However, immediately after intense exercise potassium levels fall while catecholamine levels remain elevated leaving the heart vulnerable to

catecholamine induced arrhythmogenesis (Paterson 1996). In addition development of exercise-associated arrhythmias has been associated with a tendency for a higher blood lactate value (Jose-Cunilleras *et al.* 2006) which is likely to occur in longer races.

Age

The odds of sudden death increased 1.3 fold with every 1 year increase in age. Unfortunately it is impossible to separate the effect of age from time in training as there were no untrained controls and training data were not available for investigation. Cardiac electrophysiological changes are well recognised as a result of cardiac hypertrophy secondary to athletic training in humans with frequent and complex ventricular ectopy being common in human athletes (Hart 2003). Cardiac remodelling (hypertrophy) has been identified in horses in athletic training (Buhl *et al.* 2005a, b; Young 1999). The increased risk of sudden death with age may therefore be partly explained by increased time in training as it is possible that cardiac hypertrophy may also lead to increased risk of fatal cardiac arrhythmia in horses. However, age was not associated with development of exercise-related arrhythmias in one treadmill study (Jose-Cunilleras *et al.* 2006).

Exercise-associated epistaxis has been reported to be more common in older horses in some studies (Takahashi *et al.* 2001; Weideman *et al.* 2003) and increased risk of EIPH may therefore contribute to the increased risk of sudden death associated with increased age. Conversely though, some other studies have not associated epistaxis/EIPH with increased age (Hinchcliff *et al.* 2010; Newton *et al.* 2005). The recurrence rate of epistaxis has been estimated at 13.2% (Takahashi *et al.* 2001) and it has been suggested

that some cases of sudden death may be fulminant cases of EIPH (Gunson *et al.* 1988). Recently regional pulmonary veno-occlusive remodelling has been identified in EIPH although it remains unclear whether this pathology relates to cause or effect (Williams *et al.* 2008). Accumulation of pathology such as veno-occlusive remodelling with age could explain the increase in incidence of EIPH associated with age in some studies.

Similarly accumulation of microscopic cardiac pathology such as cardiac fibrosis with age may increase the risk of development of fatal cardiac arrhythmia. Ventricular fibrillation is more likely to develop when acute cardiac ischaemia is superimposed on a healed infarct. This has been used to produce animal models to study the pathophysiology of cardiac arrhythmias (Paterson 1996). In addition the efficacy of mutual antagonism is reduced when hyperkalaemia, acidosis and increased noradrenalin are superimposed upon a heart with regional ischaemia or a small infarct (Paterson 1996). Gross and microscopic myocardial fibrosis have been reported as an incidental finding in horses at post mortem(Cranley and McCullagh 1981; Else and Holmes 1972a, b) but no association with age was detected in these studies. Currently neither the role of myocardial fibrosis in arrhythmogenesis in the horse nor the true prevalence of this lesion in any age-group is known.

Arterial wall fibrosis has been associated with peripartum uterine artery rupture in mares, and this condition has been associated with increased age (Ueno *et al.* 2010). Similar age-related degenerative changes may occur in other blood vessels and predispose to arterial rupture described as the cause of sudden death in some cases (Lyle *et al.* 2011).

Calcification of the tunica media of the large arteries has been reported as a common finding in *young* Thoroughbred racehorses (mean age 3.84 +/-0.30 years), particularly affecting the pulmonary arterial branches (Arroyo *et al.* 2008). It has been suggested that this may lead to rupture of these vessels due to reduced vascular compliance. However although pulmonary haemorrhage is commonly described in post mortem examination of sudden death cases, rupture of the pulmonary arteries is rarely reported. In cases of sudden death attributed to vascular rupture, abdominal vessels have been reported to be more common and there is often no pathology associated with the site of rupture (Lyle *et al.* 2011).

The number of career starts was not associated with increased risk of sudden death either at univariable level or when forced into the final multivariable model. This suggests that increased exposure time at risk did not contribute to the increased risk associated with age. A limitation of the current study was the lack of data on exercise during training. It is possible that exposure time during racing is too crude a measure of overall exercise exposure to demonstrate an association with sudden death. Further investigation of total exercise exposure time (in both racing and training) would be justified in future studies.

Race-type

Increased odds of sudden death were observed in hurdle and steeplechase races compared with flat races. Horses competing in steeplechase races have previously been identified at greater risk of epistaxis (Newton *et al.* 2005; Takahashi *et al.* 2001), suggesting an increased prevalence of EIPH in steeplechasers. This has been attributed to increased

locomotory impact-induced trauma (Newton *et al.* 2005). Jump races are likely to be more strenuous than flat races so hurdlers and steeplechasers may develop more marked metabolic derangements. This may contribute to development of arrhythmias as described earlier. In addition heart rate is more likely to fluctuate during jump races then flat races. Changes in heart rate may be associated with increased propensity for VPCs due to changes in autonomic tone (Physick-Sheard and McGurrin 2010). Larger heart size in this group compared to horses racing in flat races (Young *et al.* 2005) may also predispose to ventricular fibrillation, although type of racing was not associated with development of cardiac arrhythmias in one treadmill study (Jose-Cunilleras *et al.* 2006).

Misclassification of traumatic catastrophic injuries such as cervical vertebral fractures as sudden death cases may also have contributed to the increased odds in this group as cases were not defined at post mortem level. Given the unexpected and rapid nature of some sudden deaths and some traumatic accidents it can be difficult to accurately determine if the collapse was traumatic or non-traumatic.

Increased odds of sudden death were observed in NH flat races compared to conventional flat races. Horses that have not raced on the flat are allowed to compete in up to three NH flat races before racing over jumps. These young horses may have increased circulating levels of catecholamines secondary to their inexperience and possible psychological stress. Psychological stress has been proposed as a risk for development of post-exercise arrhythmia in horses (Physick-Sheard and McGurrin 2010) and increased catecholamine levels may predispose horses to fatal arrhythmias (Paterson 1996). Larger

heart size in this group compared to horses racing in conventional flat races (Young *et al.* 2005) may also predispose to fibrillation. In addition these horses may be less fit and therefore predisposed to fatal arrhythmias. High vagal tone secondary to training confers protection against ventricular fibrillation (Billman and Hoskins 1989; Hull *et al.* 1994; Smith *et al.* 2005). The mechanism of vagal protection against the pro-arrhythmic effects of high sympathetic tone and hypokalaemia is unknown but may occur through antagonism of calcium channels (Paterson 1996). Genetic ion channelopathies (e.g. long Q-T syndrome) and accessory pathways that cause sudden death in young human athletes (Ng and Maginot 2007) have not been identified in horses. However, if such conditions exist it is likely that they would manifest early in the horse's career and this may explain the increased risk for sudden death in this group of horses. Conversely there was no evidence of clustering within sire which might be expected if there was a genetic predisposition.

Season

Racing in the summer was associated with increased odds of sudden death. This may reflect more severe acid-base and electrolyte derangements associated with sweating in warmer weather and so increased risk for fatal cardiac arrhythmia. Conversely, racing in the spring has been associated with increased risk of epistaxis (Newton *et al.* 2005), but that study did not take into account occult cases of EIPH which had no epistaxis.

Starts in the last 60 days

Increased frequency of starts prior to the start was protective at univariable level and multivariable for all time periods investigated (30, 60, 90,180 and 365 days prior to the start). "Starts in the last 60 days" was used in the final model. Horses racing more frequently prior to the race start are likely to be fitter and these variables may therefore be proxies for athletic fitness and health (i.e. absence of illnesses that would have resulted in time off). As described earlier less fit horses may be at increased risk of fatal cardiac arrhythmia. This hypothesis may contradict the previous suggestion that exercise-induced hypertrophy may predispose horses to arrhythmias but it is possible that both long term training (as measured by age) and short-term fitness (as measured by starts in the previous 30-365 days) have an effect given the inclusion of both these variables (age and starts in the last 60 days) in the final model.

Previous risk factor studies

Previous risk factor studies for racecourse incidents that have used fatality as an outcome are heavily biased by cases of catastrophic musculoskeletal injury (Boden *et al.* 2007a, b; Boden *et al.* 2006; Henley *et al.* 2006; Williams *et al.* 2001) but have identified similar risk factors to those identified in this risk factor study for fatality due to sudden death alone.

Similar to the findings in this study increased race length (Boden *et al.* 2007a; Henley *et al.* 2006) and increased age (Henley *et al.* 2006; Williams *et al.* 2001) have been associated with increased risk for fatality. Previous studies have also identified increased

risk of sudden death in jump races compared to flat races (Boden *et al.* 2006; Williams *et al.* 2001), in steeplechases compared to hurdle races (Boden *et al.* 2007b) and in NH flat races compared to conventional flat races (Williams *et al.* 2001).Contrary to our study, Henley *et al.* (2006) identified slightly increased risk in hurdle races compared to steeplechase races. Racing in February to May was identified as a risk factor for fatality in one study (Henley *et al.* 2006) whereas racing in summer (June-August) was identified as a risk factor in the current study. In previous studies racing on firmer going was associated with increased odds of fatality compared with racing on softer ground in all race types (Henley *et al.* 2006; Williams *et al.* 2001) and in flat starts (Boden *et al.* 2007a) but was not statistically significant in jump starts (Boden *et al.* 2007b). Going was not significant at multivariable level in the current study.

Previous studies investigating fatality have identified more starts in the 60 days prior to the race as contributory in flat starts (Boden *et al.* 2007a) but protective in jump races (Boden *et al.* 2007b). Henley *et al.* (2006) reported that the risk of fatality was decreased with increased number of starts in the previous 12 months. In studies investigating fatal and non-fatal musculoskeletal injury increased frequency of high speed exercise in the 30 days or 60 days prior to the race has been identified as detrimental in some studies (Estberg *et al.* 1998a; Estberg *et al.* 1996a), protective in others (Cohen *et al.* 2000; Perkins *et al.* 2005) and non-significant in others (Parkin *et al.* 2004a, 2005b). Studies in which more frequent high speed exercise prior to the race has been protective have attributed this to the "healthy horse effect" or survival bias, in which healthier horses are more likely to be racing (Boden *et al.* 2007b; Cohen *et al.* 2000; Perkins *et al.* 2005).

Studies in which more frequent high speed exercise prior to the race has been detrimental have attributed this to accumulation of pathology (bone and soft tissue damage) that is incompletely repaired before the next start (Boden *et al.* 2007a; Estberg *et al.* 1995; Estberg *et al.* 1998a).

Increased age, racing in hurdle or steeplechase races, hard going, female sex, racing over shorter distances and colder air temperatures have all been associated with increased risk of epistaxis or EIPH (Hinchcliff *et al.* 2010; Newton *et al.* 2005; Takahashi *et al.* 2001; Weideman *et al.* 2003). However the study design used in these investigations has been very variable and some of the data is conflicting. Further investigation into EIPH events and sudden death within the same database is warranted given the high prevalence of pulmonary haemorrhage in sudden death cases shown in post mortem studies (Boden *et al.* 2005; Brown *et al.* 1988; Gelberg *et al.* 1985; Gunson *et al.* 1988; Johnson 1994a; Lyle *et al.* 2011).

Performance of the model

As with most risk factor studies, the value of this model is limited as it has not been validated on another dataset. Ideally, future studies would be implemented to validate this model on new data. In any case the number of sudden deaths that could be prevented by removal of risk factors and implementation of protective factors is likely to be minimal due to the low incidence. However as the risk factors for sudden death and fatality as a whole appear similar, such measures may be beneficial in reduction of overall fatality. There appears to be conflicting evidence as to whether racing intensity is

protective or detrimental regarding overall fatality risk as well as both fatal and non-fatal musculoskeletal injury risk so further investigation is warranted. As the frequency of fatal and non-fatal musculoskeletal injuries is much greater than the frequency of sudden death (Boden *et al.* 2006; Henley *et al.* 2006; Williams *et al.* 2001), implementation of a common factor which reduces the odds for sudden death but increases the odds for catastrophic musculoskeletal injury would be counter-productive.

In conclusion, the risk factors identified in this study were not uniquely associated with sudden death and have been also been identified in studies using fatality as the outcome. This data suggests that a generic approach to reduce fatal musculoskeletal injury and sudden death may be possible. The identification of risk factors allows speculation on the underlying mechanisms of sudden death in racing. It is hoped that this will stimulate hypothesis-led investigations into the pathogenesis of exercise-related arrhythmias, EIPH and blood vessel rupture.

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[1]Microsoft Corp, Redmond, Washington, USA

[2]StataCorp, College Station, Texas, USA

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Table 1: Descriptive statistics for continuous variables submitted to the multivariable model for sudden death in Thoroughbred racehorses in 705,913 race starts in the UK from 2000-2007

Variable	Number of Observations	Minimum Value	25th Percentile	Median Value	Mean Value	75th Percentile	Maximum Value	Linear	Best Fit
Age (yrs)	705,913	2	3	4	4.98	6	17	Yes	Continuous
Distance (km)	705,913	1	1.4	2.0	2.46	3.4	7.2	Yes	Continuous
Starts in the last 30 days	705,913	0	0	1	0.86	1	9	Yes	Continuous
Starts in the last 60 days	705,913	0	1	1	1.68	3	15	Yes	Continuous
Starts in the last 90 days	705,913	0	1	2	2.31	3	18	No	Categorical
Starts in the last 180 days	705,913	0	1	3	3.60	5	35	No	Categorical
Starts in the last 365 days	705,913	0	2	5	6.14	9	60	No	Categorical
Weight Carried (lbs)	705,913	98	123	129	134.58	149	181	No	Categorical

Table 2: Univariable analysis of variables (p value ≤0.25) submitted to the multivariable model for sudden death in Thoroughbred racehorses in 705,913 race starts in the UK from 2000-2007

Variable	Total (n = 705,913)	Cases (n = 201)	Controls (n = 705,712)	Coefficient	Standard Error	*p*-value	Odds Ratio	95% Confidence Interval
Age (yrs)	705,913	201	705,712	0.37	0.024	<0.001	1.44	1.38 - 1.51
Animal type						**<0.001**		
Neither maiden/novice	481,777	140	481,637				1 (REF)	
Maiden	121,595	13	121,582	-1.00	0.290	0.001	0.37	0.21 - 0.65
Novice	102,541	48	102,493	0.48	0.167	0.004	1.61	1.16 - 2.24
Change in run distance						**0.014**		
None	402,748	94	402,654				1 (REF)	
Increase	167,217	60	167,157	0.43	0.165	0.009	1.54	1.11 - 2.13
Decrease	135,948	47	135,901	0.39	0.179	0.028	1.48	1.04 - 2.1
Distance	705,913	201	705,712	0.74	0.053	<0.001	2.09	1.89 - 2.32
Going						**0.100**		
G, G to F, G to S, St, St to Fa, St to Sl	568,773	150	568,623				1 (REF)	
Heavy, soft, slow	111,112	43	111,069	0.38	0.173	0.027	1.47	1.05 - 2.06
Hard, firm, fast	26,028	8	26,020	0.15	0.363	0.673	1.17	0.57 - 2.37
Race time						**0.199**		
Evening	94,845	21	94,824				1 (REF)	
Afternoon or morning	611,068	180	610,888	0.29	0.231	0.216	1.33	0.85 - 2.09
Race type						**<0.001**		
Flat	448,571	34	448,537				1 (REF)	
Hurdle	146,543	71	146,472	1.86	0.209	<0.001	6.39	4.25 - 9.62
Steeplechase	89,281	87	89,194	2.55	0.202	<0.001	12.87	8.66 - 19.13
National Hunt Flat	21,518	9	21,509	1.71	0.375	<0.001	5.52	2.65 - 11.51
Season Type						**0.096**		
Spring / Autumn / Winter	496,731	152	496,579				1 (REF)	
Summer	209,182	49	209,133	-0.27	0.164	0.104	0.77	0.55 - 1.06
Starts in the last 30 days	705,913	201	705,712	-0.44	0.098	<0.001	0.64	0.53 - 0.78
Starts in the last 60 days	705,913	201	705,712	-7.78	0.098	<0.001	0.76	0.68 - 0.85
Starts in the last 90 days						**0.014**		

≤3starts	532,509	166	532,343				1 (REF)	
4 or more starts	173,404	35	173,369	-0.11	0.047	0.019	0.90	0.82 - 0.98
Starts in the last 180 days						**<0.001**		
0 - 1	223,826	93	223,733				1 (REF)	
2 - 3	181,880	42	181,838	-0.59	0.186	0.002	0.56	0.39 - 0.8
4 - 5	129,917	34	129,883	-0.46	0.200	0.021	0.63	0.43 - 0.93
6 +	170,290	32	170,258	-0.79	0.205	<0.001	0.45	0.3 - 0.68
Starts in the last 365 days						**<0.001**		
0 - 2	205,808	79	205,729				1 (REF)	
3 - 5	170,769	55	170,714	-0.18	0.176	0.318	0.84	0.59 - 1.18
6 - 9	168,972	43	168,929	-0.41	0.190	0.030	0.66	0.46 - 0.96
10 +	160,364	24	160,340	-0.94	0.233	<0.001	0.39	0.25 - 0.62
Surface						**<0.001**		
AWT	128,699	12	128,687				1 (REF)	
Turf	577,214	189	577,025	1.26	0.298	<0.001	3.51	1.96 - 6.3
Weight carried						**<0.001**		
Less than 140 lbs	449,459	45	449,414				1 (REF)	
140 lbs or greater	256,454	156	256,298	1.80	0.169	<0.001	6.08	4.36 - 8.47

P-values in bold were based on likelihood ratio tests. Other *p*-values are Wald test *p*-values.
G=good, F=firm, S=slow, St=standard, Sl=slow, Fa=fast
AWT = all weather track

Table 3: Final multivariable model for sudden death in Thoroughbred racehorses in 705,913 race starts in the UK from 2000-2007

Risk Factors for Fatality	Coefficient	Standard Error	*p*-value	Odds Ratio (OR)	95% Confidence Interval
Race Type					
Flat				1 (REF)	
Hurdle	0.78	0.31	0.012	2.18	1.19 - 4.01
Steeplechase	0.81	0.36	0.024	2.26	1.12 - 4.57
National Hunt Flat	1.14	0.42	0.006	3.13	1.39 - 7.07
Season Type					
Spring / Autumn / Winter				1 (REF)	
Summer	0.57	0.17	0.001	1.77	1.26 - 2.48
Age (years)	0.25	0.03	<0.001	1.29	1.21 - 1.37
Distance (km)	0.25	0.10	0.016	1.28	1.05 - 1.57
Starts in the last 60 days	-0.18	0.06	0.003	0.83	0.74 - 0.94

Supplementary information

Fig S1: Causal web illustrating variables submitted to the model building process.

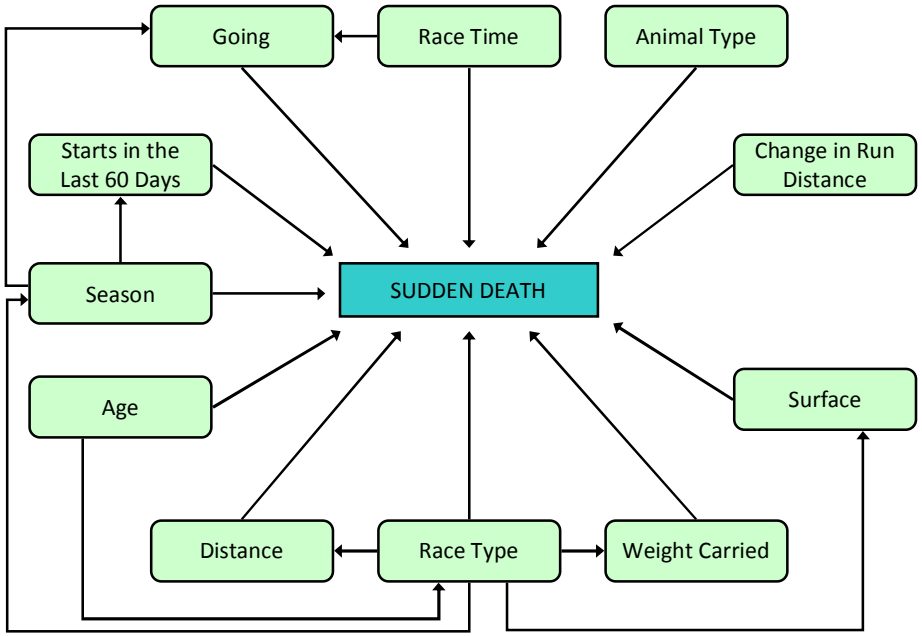

Table 4: Univariable analysis of variables (p value >0.25) not submitted to the multivariable model for sudden death in Thoroughbred racehorses in 705,913 race starts in the UK from 2000-2007

Variable	Total (n = 705,913)	Cases (n = 201)	Controls (n = 705,712)	Coefficient	Standard Error	*p*-value	Odds Ratio	95% Confidence Interval
Eye equipment						**0.751**		
Yes	623,233	176	623,057				1 (REF)	
No	82,680	25	82,655	0.07	0.214	0.749	1.071	0.7 - 1.63
Handicap						**0.411**		
Handicap	594,801	158	594,643				1 (REF)	
Weight for Age	111,112	43	111,069	-0.12	0.142	0.412	0.890	0.67 - 1.18
Race class*						**0.308**		
D and E	251,375	69	251,306				1 (REF)	
A, B and C	78,248	27	78,221	0.23	0.227	0.313	1.257	0.81 - 1.96
F, G and H	133,636	48	133,588	0.27	0.188	0.152	1.309	0.91 - 1.89
Runners in race						**0.421**		
Fewer than 20	669,271	193	669,078				1 (REF)	
20 or more	36,642	8	36,634	-0.28	0.361	0.441	0.757	0.37 - 1.54
Running sequence						**0.631**		
Late	287,621	81	287,540				1 (REF)	
Early	213,343	56	213,287	-0.07	0.174	0.686	0.932	0.66 - 1.31
Middle	204,949	64	204,885	0.10	0.167	0.537	1.109	0.8 - 1.54
Selling/Claiming						**0.273**		
Sell/Claim	637,702	186	637,516				1 (REF)	
None	68,211	15	68,196	-0.28	0.268	0.293	0.754	0.45 - 1.28
Starts ever						**0.503**		
8 or fewer	374,872	102	374,770				1 (REF)	
9 or more	331,041	99	330,942	0.09	0.141	0.503	1.099	0.83 - 1.45
Tongue strap						**0.577**		
No	670,033	189	669,844				1 (REF)	
Yes	35,880	12	35,868	0.17	0.298	0.567	1.18573	0.66 - 2.13
Total money won over career						**0.879**		

No money won	172,340	50	172,290				1 (REF)	
Money won	533,573	151	533,422	-0.02	0.163	0.879	0.97543	0.71 - 1.34
Value of race						**0.755**		
£5000 or less	358,962	100	358,862				1 (REF)	
More than £5000	346,951	101	346,850	0.04	0.141	0.755	1.044978	0.79 - 1.38

*Race class data were only available for some of the dataset as this classification was stopped in 2005.