

PROJECT/STUDY TITLE:	Investigating Equine Disease Using Multicentre Electronic Medical Record Analysis
PRINCIPAL APPLICANT(S)	Dr. John F. Marshall, Dr. Tim D. H. Parkin
GRANT AWARDED (DATE):	04/01/15

Lay summary of project outcomes, achievements and potential impact: Max 300 words

Our project used advanced statistical methods to answer important questions about a range of chronic diseases in the horse. We determined how common diseases are, what diseases occur together (comorbidity) and crucially what effect diseases have on the life expectancy of horses. We did this by analyzing large databases of medical records from horses in the UK (70,477 horses) and USA (138,175 horses). Laminitis (founder) and endocrine diseases (Cushing's disease) were the most common conditions in our database and commonly occurred together. In fact, laminitis is involved in over 70% in horse's suffering from more than one disease. Knowing how common diseases are will aid in educating horse owners and vets and prioritizing future research. We found strong evidence for increasing life expectancy among horses in the UK; a horse born between 2010 and 2012 can be expected to live for almost 25 years. This is valuable information for horse owners and vets when making decisions about horses in their care. Next, we quantified the effect of specific diseases on life expectancy. We validated our analysis techniques by looking at horses without disease and those with grass sickness, a disease that is often fatal. As expected, horses without disease had a normal life expectancy, while those with grass sickness had a dramatically reduced life expectancy. Interestingly, endocrine diseases caused the most significant effects on life expectancy after grass sickness, followed by cancer and laminitis. We were also able to quantify the additional risk of death associated with having more than one chronic disease; horses with two diseases or three diseases are seven or twenty-one times more likely to die than a horse without chronic disease respectively. Crucially, we also found evidence that the proportion of horses with more than one chronic disease is increasing every year.

Detailed progress against original objectives: List outcomes against original objectives. Discuss what has been achieved, including any statistical analysis completed as part of the project.

Aim 1: Determine the prevalence of significant diseases affecting the welfare of the veterinary-attended population of horses in the UK and North America.

- 1. Disease syndrome definition, dictionary construction and preliminary analyses are complete.** This work has generated multiple highly sensitive dictionaries for the identification of cases of more than ten diseases across both UK and US datasets. UK-based dictionaries were constructed using the entirety of the available data to maximize sensitivity and specificity, and US dictionaries were constructed on one fifth of the US dataset to expedite analysis whilst retaining sensitivity. Nearly 9000 cases of chronic disease were identified in the UK data, including 6103 horses with laminitis.
- 2. Disease prevalence has been analyzed for both the UK and US datasets.** The prevalence of ten chronic diseases including laminitis and grass sickness were ascertained relative to the size of the veterinary-attended population in the UK and US. The UK data was published in the peer-reviewed journal *Preventative Veterinary Medicine* [1] and a manuscript describing the US data is currently under review.

Aim 2: Identify patterns of comorbidity and novel risk factors for the development of laminitis.

- 3. Comorbidity has been analyzed for the UK and US datasets.** Comorbidity analyses have been conducted, which show that laminitis is a feature in over 70% of cases of disease comorbidity. Patterns of comorbidity for major equine disease syndromes have been described and published [1].
- 4. The relationship between corticosteroid administration and laminitis has been explored using the most advanced statistical methodologies yet applied to the question.** Extensions to Cox proportional hazards models for repeated events were applied to the UK data to generate the most robust answer to this question yet published in veterinary medicine. We were able to quantify the effects of different corticosteroids whilst taking into account pre-existing inflammatory or endocrine disease. Over seventy percent of horses that were diagnosed with laminitis suffered at least one recurrence. Risk factors for first and subsequent laminitis episodes were found to vary (Table 1 & Table 2). Corticosteroid use (prednisolone only) was significantly associated with subsequent, but not initial laminitis episodes. This work was recently published in the peer-reviewed journal *Preventative Veterinary Medicine* [2].

Table 1: Association between potential risk factors and time to first laminitis episode in a veterinary-attended UK horse cohort between 1987 and 2013. Hazard ratios are derived from a multivariable Cox survival analysis of time to first laminitis episode.

Characteristic		Number of horses	Hazard Ratio	95% Confidence Interval	Wald <i>p</i> -value
Breed	Unknown/other	59681	1 (REF)		
	Arab	954	1.80	1.37 – 2.34	<0.01
	Cob	2132	1.36	1.10 – 1.69	<0.01
	Draught	1049	0.94	0.66 – 1.33	0.72
	Native	2218	2.46	2.10 – 2.87	<0.01
	Pony	1415	1.77	1.43 – 2.20	<0.01
	Welsh	3032	2.56	2.23 – 2.94	<0.01
Disease syndrome	Pituitary Pars Intermedia Dysfunction (PPID)	2070	11.18	9.26 – 13.51	<0.01
	Equine Metabolic Syndrome (EMS)	143	8.06	5.79 – 11.20	<0.01
	Gastrointestinal	7760	2.57	2.22 – 2.98	<0.01
	Orthopaedic	1839	1.85	1.59 – 2.16	<0.01
	Dermatologic	4473	3.70	3.03 – 4.52	<0.01
	Systemic	2778	1.35	1.19 – 1.53	<0.01
	Respiratory	3773	1.17	1.04 – 1.32	<0.01
	Recurrent Airway Obstruction (RAO)	1228	1.44	1.21 – 1.70	<0.01
Sex	Female	26019	1 (REF)		<0.01
	Male	37975	0.88	0.82 – 0.94	<0.01
	Unknown	6487	0.65	0.55 – 0.76	<0.01

REF referent level; **p*-values from likelihood-ratio tests comparing models with and without interaction term.

Table 2: Association between risk factors and time to subsequent laminitis episode (second to sixth episodes, n=3358 horses) in horses receiving veterinary attention from a convenience sample of UK veterinary practices between 1987 and 2013. Results are derived from a multivariable Prentice, Williams Peterson model of time to second to sixth laminitis episode.

Characteristic	Number of Horses	Hazard Ratio	95% Confidence Interval	Wald <i>p</i> -value
Pituitary Pars Intermedia Dysfunction (PPID)	721	1.63	1.31 – 2.03	<0.01

Orthopaedic	256	5.33	3.48 – 8.18	<0.01
Respiratory	383	3.10	2.08 – 4.62	<0.01
Systemic	358	2.69	1.84 – 3.93	<0.01
Prednisolone	156	5.25	2.59 – 10.63	<0.01
Neurological	83	7.20	3.11 – 16.67	<0.01
Recurrent Airway Obstruction (RAO)	294	0.62	0.45 – 0.85	<0.01
PPID : Respiratory		4.53	1.50 – 13.69	<0.01*
PPID : RAO		2.75	1.23 – 6.12	0.02*
Systemic : RAO		7.02	1.68 – 29.38	<0.01*

**p*-values from likelihood-ratio tests comparing models with and without interaction term.

Aim 3: Determine the effect of significant equine diseases, including colic and laminitis, on survival and risk factors for disease and death.

5. Survival analyses quantified the effect of disease and comorbidity on life expectancy. Comorbidity analyses were extended by the application of survival analysis to determine the effects of disease (Fig 1), and comorbidity (Fig 2), on the time to euthanasia or natural death. Using this data, the expected survival time or life expectancy following diagnosis for a range of diseases was described (Table 3). These analyses are entirely novel in equine veterinary medicine and the UK data was published in the peer-reviewed journal *Preventative Veterinary Medicine*. The results of the US database analyses are currently under review.

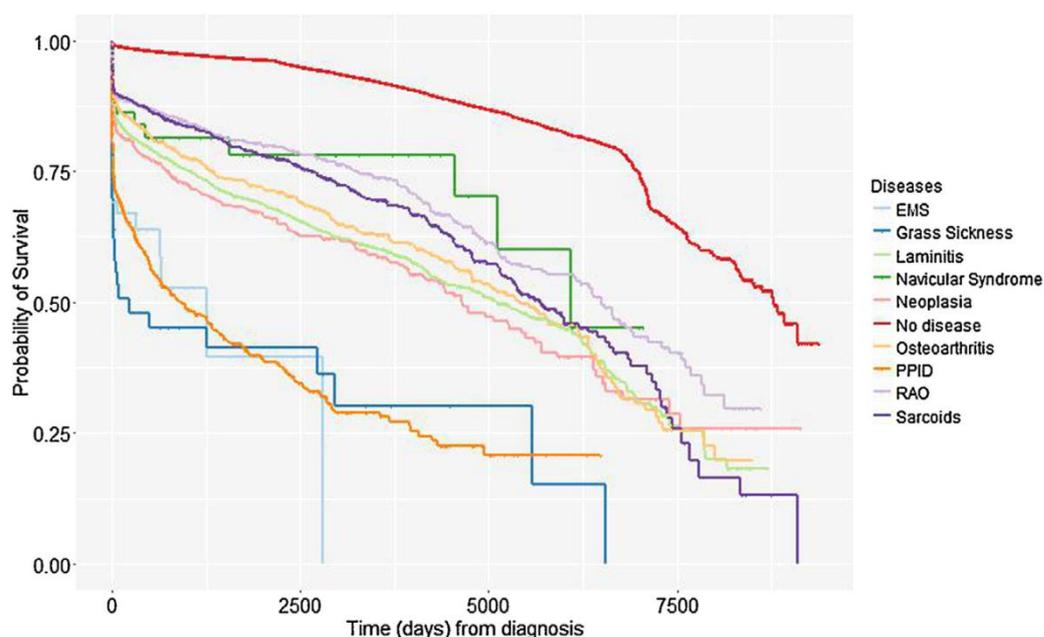


Figure 1: Kaplan-Meier survival plot of a selection of chronic diseases found to significantly affect the probability of survival in a UK veterinary attended horse population [1]. Grass sickness and endocrine diseases (PPID and EMS) were associated with the greatest decrease in probability of survival.

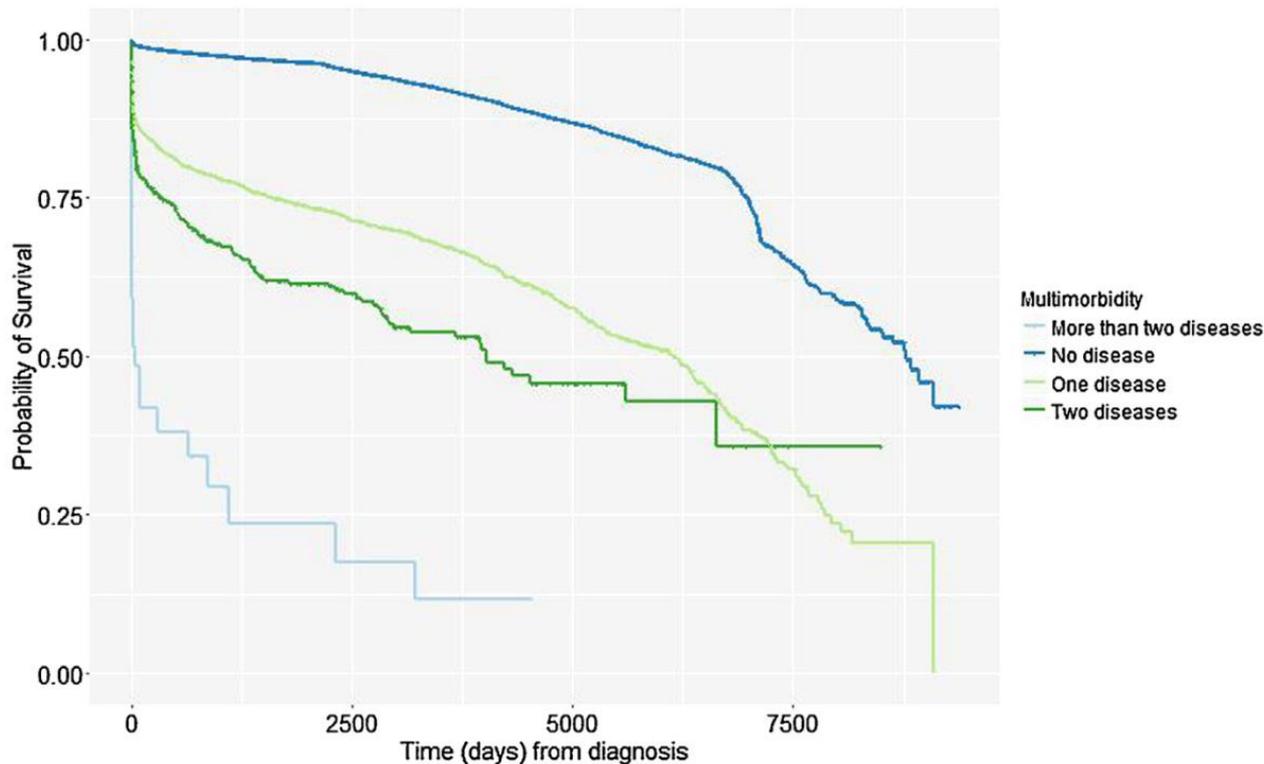


Figure 2: Kaplan-Meier survival plot of the effect of lifetime disease comorbidity status on the probability of survival in a UK veterinary attended horse population [1]. An increasing number of diagnoses directly results in a decreased probability of survival.

Table 3: Median life expectancy following diagnosis (other independent variables held at their reference or median levels).

Diagnosis	Median life expectancy in years following diagnosis (95% CI)
No chronic disease	22.7 (21.9 - NA)
Neoplasia	12.3 (11.4 – 13.6)
PPID	9.8 (9.0 - 10.7)
EMS	9.0 (7.0 - 12.4)
Grass Sickness	4.0 (2.3 – 6.8)
Laminitis	13.4 (12.7 – 14.3)
Navicular syndrome	14.4 (10.5 – 19.5)
Osteoarthritis	14.5 (13.3 – 15.9)
RAO	16.4 (15.0 – 17.9)
Sarcoids	15.4 (14.3 – 16.7)

CI confidence interval; NA estimate not available.

Were there any challenges or barriers/modifications to the project? Explain the nature of and reasons for any changes in project focus, scope, delivery, schedule or evaluation.

The project ended early (16/09/16) as Dr. Welsh moved to another Research Associate position within the University of Glasgow. However, Dr Welsh continued to work on this project and all the original aims were completed.

Provide details of knowledge transfer activities to date and any future plans/actions.

Abstract Presentations

The following oral abstract presentations were the direct result of this project. Authors supported by the NHF are in bold.

- [1] **Marshall JF. Antimicrobial Use in Equine Practice.** British Equine Veterinary Association Congress, Liverpool, UK, September 2017
- [2] **Marshall JF. Changing disease patterns in an aging horse population.** British Equine Veterinary Association Congress, Liverpool, UK, September 2017
- [3] **Welsh CE, Parkin TDH, Duz, M and Marshall JF.** Use of restricted antimicrobials in US first-opinion equine medicine. British Equine Veterinary Association Congress, Birmingham, UK Sept 2016. DOI: 10.1111/evj.41_12612
- [4] Hammersley E, Marshall JF, **Parkin TDH, Duz M, and Welsh CE.** Retrospective study of the use of reserved antimicrobials in first-opinion UK equine veterinary practice. British Equine Veterinary Association Congress, Birmingham, UK Sept 2016. DOI: 10.1111/evj.40_12612
- [5] Tay ADCM, **Parkin TDH, Duz M, Marshall JF and Welsh CE.** Distribution of fractures in the general UK equine population. British Equine Veterinary Association Congress, Birmingham, UK Sept 2016. DOI: 10.1111/evj.38_12612

Provide details of any original peer-reviewed research papers, book chapters and books/monographs that have resulted directly from your work supported by this grant.

1. Welsh, C.E., Duz, M., Parkin, T.D.H. and Marshall, J.F. (2016) Prevalence, survival analysis and multimorbidity of chronic diseases in the general veterinarian-attended horse population of the UK. *Prev. Vet. Med.* **131**, 137–145.
<http://dx.doi.org/10.1016/j.prevetmed.2016.07.011>.
2. Welsh, C.E., Duz, M., Parkin, T.D.H. and Marshall, J.F. (2017) Disease and pharmacologic risk factors for first and subsequent episodes of equine laminitis: A cohort study of free-text electronic medical records. *Prev. Vet. Med.* **136**, 11–18.
<http://linkinghub.elsevier.com/retrieve/pii/S0167587716305815>.
3. Welsh, C.E., Parkin, T.D.H. and Marshall, J.F. (2016) Use of large-scale veterinary data for the investigation of antimicrobial prescribing practices in equine medicine. *Equine Vet. J.* 1–8.

Briefly tell us about the staff who received a salary or stipend from this grant (including yourself) - Name, job title, full or part time

Dr. Claire Welsh, Research Associate (Full Time). Dr. Welsh was recruited as a research associate and received salary support from 04/01/15 to 16/09/16. She then moved to her current position as a Research Associate within the Institute of Cardiovascular and Medical Sciences at the University of Glasgow.

How has the grant contributed to the professional development of the staff named above (including yourself)? Max 250 words

Dr. Claire Welsh was recruited after recently completing her PhD in equine epidemiology. This project allowed Dr. Welsh to develop new skills and expertise that resulted in three first-author publications in high quality veterinary journals and the acceptance of an abstract accepted for oral presentation at the British Equine Veterinary Association's annual Congress in 2016. Ultimately, this project allowed Dr. Welsh to develop her career and led to her recruitment to a longer-term position within the Institute of Cardiovascular and Medical Sciences at the University of Glasgow.

Have the results been published? If yes please state when:

Yes.

1. Welsh, C.E., Duz, M., Parkin, T.D.H. and Marshall, J.F. (2016) Prevalence , survival

analysis and multimorbidity of chronic diseases in the general veterinarian-attended horse population of the UK. *Prev. Vet. Med.* **131**, 137–145.
<http://dx.doi.org/10.1016/j.prevetmed.2016.07.011>.

2. Welsh, C.E., Duz, M., Parkin, T.D.H. and Marshall, J.F. (2017) Disease and pharmacologic risk factors for first and subsequent episodes of equine laminitis: A cohort study of free-text electronic medical records. *Prev. Vet. Med.* **136**, 11–18.
<http://linkinghub.elsevier.com/retrieve/pii/S0167587716305815>.
3. Welsh, C.E., Parkin, T.D.H. and Marshall, J.F. (2016) Use of large-scale veterinary data for the investigation of antimicrobial prescribing practices in equine medicine. *Equine Vet. J.* 1–8.

Use the space below for any other relevant information you wish to report on.

In addition to completing the aims of this project, we were able to expand the scope of the project to include a preliminary study into antimicrobial prescribing practice by equine veterinary surgeons. The results of this study were presented at the BEVA Congress in 2016 and recently published in the *Equine Veterinary Journal* [3].