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1 **Liver fluke in beef cattle – impact on production efficiency and associated**
2 **greenhouse gas emissions estimated using causal inference methods**

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4

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15

16 Short title: Effects of liver fluke on cattle production

17

18 **Abstract (400 words max – 399 at present)**

19 We aimed to estimate 1) the marginal effect of liver fluke (*Fasciola hepatica*) infection
20 on productivity of Scottish beef cattle, and 2) the associated greenhouse gas
21 emissions intensity (GHG EI). Data comprised 240,065 abattoir records from NE
22 Scotland from 2014-2017, including the presence or absence of lesions typical of
23 liver fluke in the liver at the time of slaughter, from which we inferred liver fluke
24 infection status. The retrospective analysis of abattoir records to estimate marginal
25 effects of an exposure is complicated by the multi-dimensional, clustered nature of

26 the datasets, which result in confounding of potential causal factors with the
27 exposure. Causal inference methods are required to identify and correct for variation
28 in background exposure. We constructed directed acyclic graphs (DAGs) of observed
29 variables, including the potential confounders, breed, sex, breeder, finisher, season
30 of birth and year of birth. We then applied inverse probability weighting (IPW) to
31 adjust for variation among exposure risk and applied a doubly robust generalized
32 linear model (DRGLM) to the weighted observations to estimate the marginal effect
33 of fluke on the growth rate of animals and total days from birth until slaughter. We
34 compared these estimates with the results of linear mixed effects (LME) models with
35 the same variables, treating breeder and producer as random effects. To estimate
36 GHG EI, we applied IPCC tier-2 type GHG calculations to the marginal effects
37 estimated from IPW with DRGLM. The IPW with DRGLM model estimated that
38 animals with active fluke lesions (adult fluke seen on postmortem inspection) gained
39 17 (95% CI 12-22) g/d less saleable beef than animals with no lesions and no visible
40 fluke. Animals with active fluke lesions were 11 (95% CI 6.5-15) d older at slaughter
41 weight than animals with no lesions. Animals with historic lesions in which there was
42 scarring of the liver but in which no adult fluke were seen showed a wide variation in
43 effect estimates, consistent with some misclassification. The effect estimates from
44 LME models suggested slightly lower effects of fluke on growth rate and days to
45 slaughter but with overlapping 95% confidence intervals. Calculation of the
46 associated GHG emissions suggest the EI of meat from a herd with no fluke is
47 approximately 1.5% lower than the same herd with fluke. Sustainably controlling liver
48 fluke would have additional production benefits not included in this estimate and
49 could therefore have a much greater impact on GHG EI in practice than
50 demonstrated here.

51

52 **Keywords:** Liver fluke, cattle, abattoir, production impact, greenhouse gas emissions

53

54 **Introduction**

55 Ruminant livestock are responsible for approximately 50% of agricultural GHG
56 emissions in Scotland (Salisbury et al., 2015), and there is political pressure on the
57 livestock sector to reduce emissions in line with internationally agreed emissions
58 targets, for example, Scottish Government Net Zero Emissions by 2045 (Scottish
59 Government, 2019). There is also increasing societal pressure, with the consumption
60 of livestock products currently subject to criticism on the grounds of GHG contribution
61 and other perceived environmental impacts, something the supermarket sector is
62 also increasingly aware of. Endemic, production-limiting disease is a major constraint
63 on efficient livestock production, both nationally and internationally, and will have an
64 impact on the carbon footprint of livestock farming. UK systems are particularly
65 vulnerable to endemic (or production) disease impacts because they are largely
66 pasture-based, and typically utilise relatively unproductive land, classed as Less
67 Favoured Area, LFA (or Area under Natural Constraint, ANC). Some 85% of
68 Scotland's land cover is classed as LFA, ideally or only suitable for rough grazing by
69 ruminants (Scottish Government, 2018). The carbon footprint (emissions intensity, or
70 EI) of ruminant meat and milk production is sensitive to changes in key parameters,
71 such as maternal fertility rates, mortality rates, milk yield, growth rates and feed
72 conversion ratios. All these parameters are influenced by health status, so improving
73 health status would be expected to lead to reductions in EI (Eory et al., 2015;
74 MacLeod & Moran, 2017). A rapid assessment of the potential contributions to GHG
75 EI from Scottish animal agriculture that could be made by eradicating or controlling

76 12 livestock diseases, showed that all the diseases increased GHG EI (Skuce et al.,
77 2016; Bartley et al 2016).
78
79 Accurate estimates of the effects of disease on animal life-time performance are
80 required to predict the GHG EI implications of disease control. However, the effects
81 of endemic disease of livestock on production performance are difficult to quantify,
82 either relying on experimental challenge studies, which do not reflect the natural
83 presentation of many of these diseases, or on examination of opportunistic,
84 retrospective data. The liver fluke, *Fasciola hepatica*, is thought to be one of the most
85 economically important helminth parasites of grazing livestock in temperate regions,
86 with broad-brush estimates of its economic impact at £23 million per year in the UK,
87 and more than \$3 billion worldwide (Spithill et al., 1999). Previous studies on the
88 effect of fluke have yielded somewhat inconsistent results, some studies showing
89 infected animals to be relatively unaffected by fluke (Charlier et al., 2012; Bellet et al.,
90 2016), others showing a range of effects, including poor weight gain, increased
91 weight following treatment, poor fertility and poor carcass yield (Sykes et al., 1980;
92 Schweizer et al., 2005). Two studies in Scotland have previously used large sets of
93 abattoir data to quantify the impact of liver fluke (Sanchez-Vasquez and Lewis, 2013;
94 Mazeri et al., 2017). Meat inspection protocols in the UK are governed by Reg (EC)
95 2019/627, on “the uniform practical arrangements for the performance of official
96 controls on products of animal origin intended for human consumption”. Livers must
97 be visually inspected in all cases and incised if there is a suspicion of abnormalities.
98 UK abattoirs record lesions (‘faults’) as identified by the meat inspectors, providing an
99 opportunity to investigate the impact of fluke in naturally exposed animals. The study
100 of Sanchez-Vasquez and Lewis (2013) indicated that fluke infection had small effects

101 on cold carcass weight (-0.63 kg), carcass value (-£1.50), carcass fat cover, and
102 carcass conformation. Mazeri et al. (2017) showed that overall the fluke-infected
103 animals were 10 d older at slaughter, but in Holstein-Friesian animals with fluke the
104 delay in time to slaughter was 23 d. They identified problems with multi-
105 dimensionality and the lack of exchangeability of background exposure to fluke of the
106 distinct cohorts of cattle as problems that impeded effective multivariate analysis.

107

108 The histories of exposure to liver fluke vary among animals in retrospective abattoir
109 studies in a complex manner. The incidence of fluke infection in livestock varies with
110 year, season, region, and post-code area (McCann et al., 2010). There are
111 interactions of these sources of variation with the animal type, animal age, grazing
112 history, production system and the administration of flukicidal drugs. An extra
113 dimension is added by the movement of animals from one holding to another,
114 resulting in variable exposure of individuals to several systems, each with its own risk
115 of exposure to fluke. Some animals might be born on one holding, reared, grown and
116 fattened on that holding before finally being slaughtered. Other animals might travel
117 extensively from the holding of birth, to other holdings on which they might be grown
118 and fattened. Finally, animals are managed in groups, which are usually set up for
119 roughly equally sized animals to maximise feeding or other management efficiencies.
120 For example, slowly growing older animals will often be grouped and managed
121 together with rapidly growing younger animals of the same weight. In suckler herds,
122 the best performing young females will be retained for breeding stock, and the rest
123 will be sold with steers for slaughter. Consequently, the background exposures of
124 animals at slaughter are not exchangeable in an epidemiological sense, and it is
125 important to take account of potential confounding factors.

126

127 When attempting to quantify the effect of exposure to a putative risk factor on an
128 outcome variable, standard methods of multivariate regression do not effectively
129 adjust for differences among the potential explanatory variables in background
130 probability of exposure (Cole and Hernan, 2008). Directed acyclic graphs (DAGs)
131 enable explicit, *a priori* statements to be made regarding potential causal
132 relationships among the variables and thereby can identify variables that must be
133 conditioned on to minimise confounding in multivariate models (Textor et al., 2016).
134 Their construction is dependent on pre-existing knowledge or hypotheses. Inverse
135 probability weighting (IPW) methods have been developed to generate counterfactual
136 weightings for the effects of exposures where background exposure varies among
137 potential explanatory variables (Cole and Hernan, 2008). These methods are
138 common in the epidemiological literature, but there are few examples of their
139 application to livestock health and production. One recent study favourably compared
140 IPW approaches with conventional multivariate regression to quantify the effect of
141 prior bovine virus diarrhoea virus (BVDV) exposure on the probability of bovine
142 respiratory disease in feedlots (Ji et al., 2020).

143

144 In this project, we aimed to quantify the relationship between *post-mortem* lesions
145 typical of liver fluke and the growth performance of cattle, by using directed acyclic
146 graphs (DAGs) to inform inverse probability weighting (IPW) with doubly robust
147 multivariate statistical analysis on a large dataset comprising approximately 250,000
148 cattle from the NE of Scotland over the years 2014-2017. We then aimed to use
149 these estimates of physical performance effects to approximate the effect of liver
150 fluke on GHG emissions intensity.

151

152 **Material and methods**

153

154 **Description of the Dataset**

155

156 Anonymised abattoir records were provided for a total of 262083 cattle going through
157 a large Scottish abattoir over the period January 2014 to October 2017. For each
158 animal the dataset included coded information on the finisher (the final
159 owner/producer who sold the animals on to the abattoir) and the breeder of the
160 animals, breed, together with sex, date of birth, date of slaughter, and carcass weight
161 for each animal. The dataset also included a record of a range of “faults” observed
162 during processing, including lesions consistent with active and historic liver fluke
163 damage. After removal of observations with missing data for any of the variables of
164 interest, there were 240065 cattle, received from 1340 producers, of which there
165 were 16411 bulls, 90682 heifers and 132972 steers. These animals were born on
166 2492 holdings. No information was available regarding the geographic locations of
167 either the holdings on which the animals were born or on which they were fattened
168 pre-slaughter.

169

170 **Effects of fluke status on performance**

171

172 All analyses were performed using R 4.0.0 (R Core Team, 2020).

173

174 **Exposure variable:** Faults in the liver associated with fluke were used as the proxy
175 for liver fluke infection. Faults were classified as active fluke (AF), historic fluke (HF),

176 or absent (NoF) according to the practices in the abattoir at the time. AF includes
177 livers in which live adult fluke are seen and HF includes livers with fibrosis and
178 scarring but no observed adult fluke. Given that the inspection of livers is conducted
179 rapidly, with non-exhaustive incision, and that fibrotic change characteristic of historic
180 lesions can also accompany active infection, it is likely that some livers classified as
181 having historic lesions were truly active and a proportion of those classified as having
182 no fault had either active or historic infections. Neither the strength of the relationship
183 between fluke infection and presence of faults, nor the temporal dimension of this
184 relationship is well defined (Mazeri et al., 2017).

185

186 **Outcome variables:** The potential outcome variables that were available from the
187 data included measures of carcass weight, carcass conformation, and the age at
188 slaughter. The purchasing and payment policies of the abattoirs strongly influence
189 the supply of cattle, such that penalties are applied for cattle that fall outside
190 preferred weight ranges. High slaughter weight is, therefore, not uniformly desirable.
191 Because of the strong market forces to equalise carcass weight and the lack of a
192 consistent desire to maximise this variable, we did not use it as a direct outcome
193 measure. In contrast, it is almost always desirable to minimise the time required to
194 produce fat cattle for slaughter, although this variable is also affected by the
195 purchasing policies of the abattoirs, as can be seen from the irregular distributions in
196 Figure 1.a. (days alive – the number of days between slaughter date and birth date –
197 for steers, heifers and bulls). A second outcome variable was desired, to provide an
198 indication of the growth rate. The most precise measure of weight gain that could be
199 obtained from the dataset was daily dead-weight gain (DDWG), calculated by
200 dividing the hot carcass weight (kg) by the number of days alive. DDWG as defined

201 here is not a commonly used variable, and it is affected by variation in the birthweight
202 of calves, however it is derived from three directly measured variables (birth date,
203 slaughter date and dead-weight). Density plots for DDWG for the different categories
204 of animals are shown in Figure 1.b, in which it is obvious that the daily rate of gain of
205 bulls is substantially higher than that of heifers and steers. A limitation on DDWG as
206 an outcome variable is that it is affected by birth weight – given the same true rate of
207 weight gain in any two animals, the animal with the higher birthweight of the two will
208 have the higher DDWG estimate.

209

210 ***Competing explanatory variables:*** The holding from which each animal was
211 transferred to the abattoir was designated as the finisher and was denoted in our
212 data by a unique code. The holding of origin – breeder – was not directly linked with
213 the breeder code, but for each breeder and each finisher, it was possible to classify
214 them into the following categories: many breeder codes to one finisher code; one
215 breeder code to many finisher codes; one breeder code to one finisher code.
216 Category/sex, and breed of animals were recorded at slaughter. There were three
217 levels for category/sex (steer, heifer, bull) and 130 breeds were recorded, of which
218 many were crossbreeds. With crossbreeds, using official breed codes in the UK, only
219 one breed is specified, and the cross is denoted by X. For example, AA is Aberdeen
220 Angus and AAX is an Aberdeen Angus Cross – the other breed is not specified and
221 could be anything. Because of uncertainty in relation to the farmers' initial decisions
222 regarding allocation of crossbreeds and given that the main objective of allocation of
223 breed was to enable unbiased controlling of the risk of exposure of animals of
224 different breed classifications to breed, no attempt was made to collapse the
225 classifications of breed into a smaller subset of breed groups. Season of birth was

226 derived from the date of birth and classified as either spring (born January-June) or
227 autumn (July-December).

228

229 **Directed acyclic graphs (DAGs):** DAGs are mathematically formulated non-
230 parametric graphical models that can be used to identify an ‘adjustment set’ for
231 statistical models. DAGs define a confounder as a purported ancestor (i.e. cause) of
232 both the exposure and the outcome, and they can be used to identify the set of
233 confounders that must be adjusted for in subsequent analysis. Similarly, they enable
234 the identification of variables which should not be adjusted for in analysis, such as
235 mediators of the exposure, or so-called ‘colliders’ (adjusting for colliders introduces
236 bias). The DAG was constructed and analysed using DAGitty (Textor et al., 2016),
237 and identified year of birth, season of birth, breeder, finisher, and category as
238 adjustment variables that potentially confounded the effect of fluke on days alive and
239 on DDWG (the DAG is shown in Figure 2). Breed was not identified as a potential
240 confounder, so was not included in the analyses using IPW to estimate the marginal
241 effect of fluke exposure but was included in multivariate models to provide an
242 indication of its relative effect. Modelling covariates for this purpose is appropriate
243 when they are on a different causal pathway to the exposure-outcome relationship
244 altogether, and so are not mediators, as was the case for breed in the DAG
245 (Ferguson et al., 2020).

246

247 **Descriptive statistics and univariate associations:** Histograms and density plots
248 were used to examine the distributions of the continuous variables. Background
249 exposures for fault (an ordinal categorical variable) were determined for each of the
250 potential explanatory variables (all categorical – year of birth, season of birth,

251 category, breeder, finisher, breed) using chi-square tests of proportions applied to
252 categorical variable pairs. The univariate relationships between each of the potential
253 explanatory variables (all categorical) and the outcome variables were tested using
254 one-way analysis of variance.

255

256 ***Inverse probability weights (IPW) and estimation of doubly robust confidence***
257 ***intervals for the marginal effect of fault on DDWG and days alive:*** To deal with
258 computational demands of the model and the dataset, the IPW analysis on the large
259 dataset was conducted on a Linux workstation with 256 Gb of RAM. In IPW, a
260 regression of the outcome of interest on the exposure of interest is undertaken with
261 observational data, with each observation weighted by the inverse of the probability
262 of the observed exposure level given the observed values of all the potential
263 confounders (van der Wal & Geskus, 2011). This process reduces the bias that
264 otherwise results from unequal exposure of covariate clusters to the factor of interest
265 (unequal exposure here is also referred to as non-exchangeability of background
266 risk). We used the package 'ipw' in R (van der Wal & Geskus, 2011) to calculate
267 weightings, and applied the weightings to a generalized linear model using the
268 function 'svyglm' in the package 'survey' for R (Lumley, 2004; Lumley 2020) to derive
269 the estimates and confidence intervals for the marginal effect of fault on the outcome
270 variables. These estimates can be considered 'doubly robust' as our modelling used
271 both IPW data and a propensity score as a covariate in the marginal models.
272 Weightings were determined for several reduced datasets to deal with problems
273 associated with aliasing of breeder and producer. In the full dataset of 240065
274 animals, there were 2492 distinct breeders, and 1340 distinct producers. The
275 complexity of the relationship between breeder and finisher in this dataset is implied

276 by the two histograms in Figure S1, and the enormous range in leverage of individual
277 breeders and finishers can be seen from the histograms in Figure S2 (ranging from 1
278 - 15218 animals per finisher) . Analysing the full dataset with no restrictions meant
279 that breeder and finisher were completely aliased in many cases, resulting in very
280 poor model performance. In contrast, if the dataset were restricted such that only the
281 cases in which there was a one-to-one correspondence, the total number of
282 observations was small (16665), with loss of representation of some of the important
283 variables, and the resulting models were weak. To deal with this problem, we
284 considered subsets of the data by including only those data for which there was a
285 minimum number of breeders for each finisher. We selected 10, 50, 100, and 500 as
286 the minimum numbers of breeders/producer, and we also performed IPW with the full
287 dataset (ie threshold = 1 breeder), and with those for which there was a one-to-one
288 correspondence. To determine the weightings, we used the 'ipwpoint' function, set for
289 ordinal exposure variables (no fault, historic fault, active fault), using the logit link
290 function, with an unstabilised numerator.

291

292 ***Multivariate analysis using linear mixed effects model:*** For completeness, four
293 linear mixed effect models were applied to the full dataset of 240065 and to the
294 reduced datasets to obtain approximations of the effects of fluke and the competing
295 explanatory variables (year of birth, season of birth, category, breed, breeder,
296 producer) on DDWG and days alive. For each analysis the 'lme' function in R was
297 used, with year of birth, season of birth, category and breed as fixed effects and
298 producer and breeder as random effects.

299

300 ***Quantifying the greenhouse gas emissions effects:*** The emissions intensity (EI,
301 the kgCO₂e per unit of output) was calculated for a Scottish beef system under the
302 three scenarios described previously (i.e. no fluke, active fluke, historic fluke) using
303 the Scottish Agricultural Emissions Model (SAEM, MacLeod et al. 2018). SAEM
304 includes the emissions arising on-farm, and the emissions arising pre-farm (from the
305 production of inputs such as feed, fuel and fertiliser). It is based on GLEAM (FAO
306 2018) and uses a predominantly IPCC 2006 Tier 2 approach (Penman et al., 2006) to
307 calculating emissions, i.e. key processes such as feed consumption and excretion
308 rates are calculated based on the livestock characteristics within a particular
309 production system. It also uses a herd model to determine herd structure and
310 dynamics which, in combination with the Tier 2 approach, enables the model to
311 reflect the particular features of Scottish systems. In order to estimate the effect on
312 EI, three scenarios were created with the weights, ages at slaughter and ages at first
313 calving corresponding to: (a) no cattle having fluke; (b) all cattle in the herd having
314 historic fluke; and (c) all cattle in the herd having active fluke. The average ages and
315 weights at slaughter for each scenario were taken from the full set of 2492 breeders,
316 1340 finishers, and 240065 animals (16411 bulls, 90682 heifers, 132972 steers). The
317 liveweight at slaughter was calculated assuming a ratio of carcass weight to
318 liveweight of 56% and the growth rate was calculated assuming a calf liveweight at
319 birth of 50 kg. The age at first calving in the no fluke scenario was derived from
320 Gates (2013). For the active and historic fluke scenarios it was assumed that that the
321 change in the age at first calving would be inversely proportional to change in growth
322 rate.

323

324 **Results**

325

326 **Effects of fluke infection status on performance**

327 In the full dataset of 240065 animals, 7048 (2.9%) were classified as having active
328 fluke faults, 42386 (18%) with historic faults, and 190631 (79%) with no faults. Each
329 of the variables from the minimum adjustment set of variables (year of birth, season
330 of birth, category, breeder, finisher) plus breed (not in the minimum adjustment set)
331 was strongly associated with both the exposure (fault) and the outcome variables of
332 DDWG and days alive, ($p < 0.0001$, univariate data not shown); Figures S3-S6 show
333 examples of relationships between each of the variables and DDWG. This indicated
334 that background variables were not exchangeable in these data (i.e. that the
335 exposure-outcome relationship was confounded by these background variables), and
336 so analysis should deal with confounding (e.g. by using IPW).

337

338 Table 2 lists summary results from IPW with DRGLM and LME and compares the
339 results from the present study with some of those from Mazeri et al. (2017). For ease
340 of reading the table only shows the contrasts between AF and NoF – in almost all
341 cases AF effects were stronger than or similar to HF relative to no fluke (NoF). The
342 highest marginal effect estimates (and the widest confidence intervals) for NoF
343 contrasted against AF for DDWG and for days alive were obtained using IPW and
344 DRGLM on the full dataset of 240065 animals. Conversely the smallest marginal
345 effect estimates were obtained using IPW and DRGLM with the dataset in which
346 were included only those cases for which there was a one-to-one correspondence
347 between breeder and finisher. All other models using IPW and DRGLM provided
348 broadly consistent results, with marginal effect estimates ranging from 32 g/d and 16
349 g/d for DDWG and -18 d to -11 d for days alive. The models in which cases were

350 included only when they came from a finisher with 10, 50 or 100 breeders supplying
351 them provided very consistent estimates of the marginal effects – 17 g/d DDWG and
352 -11 d for days alive. Figure 3 and Figure 4 show the effect estimates and the
353 confidence intervals for each of the analyses for DDWG and days alive respectively.
354 False convergence was a problem with many of the LME models but in those cases
355 where meaningful results were obtained, LME provided effect size estimates for fluke
356 infestation that were slightly lower and had narrower confidence intervals. Table 2
357 and Figure 4 show the results from Mazeri et al. (2017) for comparison.

358

359 The results of LME models conducted to obtain approximations of the effects of the
360 competing explanatory variables (year of birth, season of birth, category) on DDWG
361 and days alive are summarised in Table 3. Heifers and steers both grew at a lower
362 rate than bulls (-0.29 and -0.25 kg/d respectively). Calves born in spring grew slightly
363 more slowly than calves born in autumn (-0.0035 kg/d). Calves born in each year
364 after 2011 grew faster than those born in the preceding year (0.018 kg/d – Figure
365 S3). The effect of breed on DDWG was strong, ranging from -0.24 kg/d to 0.55 kg/d.
366 The effects of breeder and finisher were also very strong, ranging from -0.31 to 0.82
367 kg/d and -0.16 to 0.32 kg/d respectively. Figures S4-S6 show ordered coefficients for
368 breed, breeder and finisher, with histograms for their distributions after adjustment for
369 category (bull, steer, heifer). Similar results were obtained for estimates of the effect
370 of these variables on days alive (data not shown).

371

372 **Greenhouse gas effects**

373 To estimate the effect on EI, three scenarios were created with the weights, ages at
374 slaughter and ages at first calving corresponding to: (a) no cattle having fluke; (b) all

375 cattle in the herd having historic fluke; and (c) all cattle in the herd having active fluke
376 (Table 1). There was an increase of approximately 1.5% in EI arising from the
377 presence of fluke (Table 4). This arises because changing growth rates lead to
378 changes in the proportions of dietary energy used for different functions in growing
379 cattle. When the growth rate is decreased, a smaller proportion of the energy intake
380 is used for growth, i.e. the slower growing animal will, all else being equal, produce
381 less liveweight gain per MJ of feed intake (and per unit of methane, N or volatile
382 solids excreted). This leads to higher emissions per unit of output.

383

384 **Discussion**

385 Despite widespread recognition of the role of animal health and production-limiting
386 disease as a constraint on efficient livestock production, there is relatively little
387 empirical evidence to enable quantification of its effects. In this study, we used an
388 opportunistically obtained dataset to try to quantify the effects of liver fluke, one of the
389 most prevalent and important endemic diseases of livestock in temperate regions, on
390 productivity and GHG EI of animals at slaughter. Liver fluke infection as indicated by
391 liver fault status at slaughter resulted in a clearly evident reduction in the rate of gain
392 in carcase weight, with active fluke infections responsible for a reduction of 17 g/d,
393 and requiring an average extra 11 days to slaughter. Our marginal effect estimates
394 were slightly higher than those obtained for all cattle by Mazeri et al. (2017), but
395 slightly lower than those they obtained from Holstein-Friesian cattle. As a result, if all
396 other factors were equal, the EI of meat from animals with no fluke infection would be
397 approximately 1.5% lower than the same animal with fluke. However, it should be
398 noted that the 1.5% reduction in this study only takes into account the observed
399 effects on growth rate of those animals that did achieve slaughter weight. Reducing

400 fluke infections is likely to have a range of other effects (such as improved feed
401 efficiency) that would further reduce the EI. Fluke infection, as indicated by the
402 presence of either active or historic faults, accounted for about 3% of the mean for
403 DDWG, with 2% for days alive, and for about 2% of the total range in each variable.
404 In comparison, breeder, finisher, category and breed had more substantial effects
405 (Table 3); the effect of year of birth was slightly smaller, whereas season of birth had
406 a relatively much smaller effect.

407

408 Although our observations were based on a similar population of cattle to that used
409 by Sanchez-Vazquez and Lewis (2013), we selected different outcome variables
410 from those researchers. They used weight at slaughter, carcass price, carcass
411 conformation and fat cover. Because the weight at slaughter is largely predetermined
412 by the market, we didn't consider it to be a useful outcome variable. Similar
413 judgements apply to carcass price and fat cover. As a result, direct comparison of
414 our findings with those of Sanchez-Vazquez and Lewis (2013) is difficult. In contrast,
415 our project was informed by the study of Mazeri et al. (2017), who noted that it would
416 be useful to apply causal inference (CI) methods such as instrumental variable
417 analyses to better quantify the causal effect of fluke infection on animal performance.
418 We sought to apply CI to a similar dataset to theirs by first constructing a DAG to
419 identify confounders, mediators, competitors and potential instrumental variables,
420 taking fault as the exposure variable and either days to slaughter or DDWG as the
421 outcome variables. No potential instrumental variables were identified, but a
422 minimum adjustment set was proposed, which enabled the application of inverse
423 probability weighting to ensure that variation in background levels of exposure in
424 population subsets was exchangeable. In their study, Holstein-Friesian cattle with

425 rejected livers required an additional 23 d (95% CI 15-31 d) but over all other breeds,
426 the effect was 9 d (95% CI 8-11). Our estimates fall within this range. The large
427 variation of effect estimate for fluke by breed in their study suggests either breed-
428 dependent variation in susceptibility to the pathogenic effects of the fluke, or breed-
429 dependent variation in exposure to fluke. The latter explanation appears more likely,
430 given the lack of evidence of breed effects on tolerance of liver fluke infection and the
431 known different trajectories and backgrounds of dairy-derived calves going into beef
432 production. Mazeri et al. (2017) used a breed-subset approach to deal with differing
433 background exposure, whereas we applied IPW, which addresses variation in
434 exposure to fluke with all the potentially confounding covariates. Other points of
435 difference between our study and their previous study include the fact that they used
436 a weight-adjusted age at slaughter in place of our days alive and DDWG.
437 Conceptually, our DDWG is a similar measure to their weight-adjusted age at
438 slaughter, both variables taking equal account of age at slaughter and weight at
439 slaughter. Neither variable is ideal, as both are subject to simultaneity bias. Our DAG
440 resulted in the same adjustment sets for both days to slaughter and DDWG. We
441 chose to analyse the two variables separately primarily to enable the GHG EI
442 analysis. In our study there was some inconsistency in the ranking of the adverse
443 effects of active and historic faults between DDWG (higher for active) and days alive
444 (higher for historic), although the differences were always small. It is possible that
445 this might reflect temporal progression in the effects of developing fluke infections,
446 but it seems more likely that the distinction between active and historic lesions is
447 biologically spurious.
448

449 Application of the IPW method together with ‘doubly robust’ estimators of the
450 marginal effect have been shown to provide more precise effect estimates than
451 multiple regression in a study to estimate the effect of prior exposure to BVDV on the
452 probability of bovine respiratory disease (Ji et al. 2020). In that study on bovine
453 respiratory disease (BRD) in feedlot cattle, the authors applied DAG to determine the
454 minimum adjustment sets of covariates for their analysis and augmented their
455 observational study with simulated datasets based on the underlying distributions in
456 their population. They estimated marginal odds ratios of disease in animals that had
457 been exposed (seropositive) or not exposed (seronegative) to bovine virus diarrhoea
458 virus (BVDV) according to blood sampling conducted on arrival at the feedlot. They
459 compared the results derived from standard multiple regression with inverse
460 probability weighting (IPW) and inverse conditional probability weighting (ICPW)
461 methods, with or without doubly robust effect estimation, and found that the best
462 unbiased estimator for the marginal odds ratio for BVDV exposure was obtained from
463 the combination of inverse probability weighting (both conditional and non-
464 conditional) with the doubly robust methods. There were only minimal differences
465 between IPW and ICPW methods, but both methods always improved model
466 predictive power and reduced bias when compared with standard multiple regression
467 analysis. When our full dataset was analysed using a linear mixed effects multiple
468 regression (REML) approach in which finisher and breeder were included in the
469 models as random effects, with all other covariates as fixed effects, the estimates of
470 the effects of fault were quite similar to the IPW with doubly robust estimation – 15 v
471 20 g/d and 18 v 14 additional days for active fluke contrasted with no fluke. However,
472 within the IPW with DRGLM methods, because of the complex relationship between
473 breeder and finisher, some degree of restriction was required to ensure that balance

474 was maintained between breeder and finisher to prevent excessive leverage from the
475 extreme finisher ~ breeder relationships. We therefore conclude that for the
476 determination of marginal effects of fluke in our dataset, the most suitable analytical
477 approach is the IPW with DRGLM, which provided broadly similar estimates of the
478 marginal effect of acute and historic faults to a linear, mixed effects model, but for
479 which the potential confounders identified in the DAG were most explicitly and
480 transparently managed.

481

482 A 1.5% increase in GHG EI due to liver fluke would appear to be relatively modest,
483 especially when compared to the 10-30% increases estimated to result from
484 gastrointestinal nematode (GIN) parasitism in sheep (Kenyon et al., 2013; Houdijk et
485 al., 2016; Fox et al., 2018). Similarly, the effect on liveweight gain was also markedly
486 greater for cattle GIN than fluke in the Bellet et al., (2016) abattoir study in England
487 and Wales. We have only examined one aspect of fasciolosis in the present study
488 (reduced growth rates), and this is a particularly strong impact of GIN, because they
489 directly affect the host animal's appetite. However, with fluke, other effects include
490 changes in feed conversion ratio, mortality and fertility, reproductive performance,
491 milk yields and quality of output (Skuce and Zadoks, 2013), so removing the
492 challenge of fluke would be expected to have a much greater impact on EI in practice
493 than indicated by our estimates.

494

495 We are likely to have under-estimated the effect of fluke infection on the growth of
496 animals destined to be slaughtered for beef for the following reasons. 1) Animals that
497 die of fluke infection are not included in the analysis. The data we used are censored
498 such that only those cattle that survive until they reach commercially viable slaughter

499 weight are included. We cannot assess the mortality that is directly attributable to
500 liver fluke in cattle nor the number of animals that might have been culled early for
501 poor performance. 2) Growth rate effects are averaged over the animals' whole lives
502 rather than from the time of infection until slaughter, and the time of infection in
503 relation to slaughter is unknown. This problem is discussed well elsewhere (Mazeri et
504 al., 2017), and it can result in a form of simultaneity bias – there is an increasing risk
505 of infection as an animal ages, which might slow growth rates, but a more slowly
506 growing animal will also have a higher probability of exposure to infection because it
507 is held for longer to attain the target slaughter weight. Multiple ownership of cattle is
508 common – some animals are born, grown out, and fattened on one farm, but most
509 animals change ownership at least once before slaughter. Farmers also tend to
510 group animals according to performance (slowly growing older animals will be
511 grouped with faster growing younger animals of a similar weight to allow efficient
512 nutritional management). Averaging of the effects over the whole of life, together with
513 the grouping practices used by farmers will tend to decrease the effect estimates for
514 fluke infection. 3) An unknown proportion of animals with fluke infections has
515 detectable lesions in the liver at slaughter, and not all animals with lesions have truly
516 been infected. It is estimated that the sensitivity of liver inspection in abattoir is 68%
517 and its specificity is 88% (Mazeri et al., 2016), and as noted previously, using the
518 detection of faults in routine meat inspection as our proxy for fluke exposure results
519 in substantial dilution bias and diminution of the effect estimate (Mazeri et al., 2017).
520 Liver inspection at slaughter ranked fifth of five as an indicator of genuine fluke
521 infection, after veterinary inspection, serum ELISA, coproantigen ELISA and faecal
522 egg counting (Mazeri et al., 2017). This is mainly due to the speed of the abattoir line
523 and the operative having only seconds to make a judgement call on fluke

524 positive/negative and active/historic. 4) Our classification system has three levels,
525 which probably do not correspond well with the severity of infection and preclude an
526 ordinal or quantile regression approach to analysis. 5) In addition to the biasing
527 effects noted above, our analysis does not address the likely effects of fluke on the
528 fertility of animals retained for breeding, reduced feed conversion efficiency, reduced
529 fertility, milk yields or quality of output (e.g. carcass conformation and rates of liver
530 condemnation). These production parameters will also impact biological efficiency
531 but could not be quantified here, although they are expected to have an additive
532 effect on GHG EI. The net result of all the limitations listed above would be expected
533 to be a diminution of the effect estimate because of regression dilution bias.

534

535 In conclusion, we have attempted to quantify the impact of liver fluke infection in
536 terms of direct production losses and associated GHG emissions, using a large
537 database of naturally exposed animals. To deal with the variation in background
538 exposure of groups of cattle to liver fluke and the multiple confounding factors, we
539 applied inverse probability weighting and doubly robust regression analysis to the
540 data, resulting in estimates of the effect of fluke that are broadly consistent with
541 previous estimates from a similar production system and dataset.

542

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550 RD229/236 livestock stakeholder group.

551

552 **Declaration of interest**

553 The authors declare no conflicts of interest.

554

555 **Ethics statement**

556 As this study utilised data already captured from animals at the time of slaughter
557 ethical approval was not required.

558

559 **Software and data repository resources**

560 R Core Team (2020). R: A language and environment for statistical computing. R

561 Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R->

562 [project.org/](https://www.R-project.org/)

563

564 **Supporting Data**

565 Anonymised data are available from the first author on reasonable request.

566

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672

673 **Figure captions**

674

675 Figure 1. Top: Density plot of days alive for steers, heifers and bulls. Asymmetric
676 distributions are a consequence of abattoir buying patterns. Bulls younger than 500 d and
677 other cattle younger than 900 d receive a premium price, resulting in sharply truncated
678 distributions on these boundaries. Bottom: Density plot of daily deadweight gain (DDWG,
679 kg/d) for steers, heifers and bulls. Growth rates in bulls in UK systems are substantially
680 higher than those of steers and heifers.

681

682 Figure 2: Directed acyclic graph including the variables in the model. The green symbol with
683 triangle is the exposure variable (Fault); blue symbols with "I" are the outcome variables of
684 days alive and daily dead-weight gain (DDWG); blue symbols without "I" are ancestors of the
685 outcome variables (therefore, competing variables); pink symbols are potential confounders
686 (ancestors of the exposure variable and the outcome variables). Grey symbols are
687 unobserved variables. Green edges are causal paths and pink edges are biasing paths. Here
688 fluke represents the true state of fluke exposure we are using the observed variable of fault
689 as proxy for exposure to the true fluke state.

690

691 Figure 3: Marginal estimates and 95% confidence intervals for the effect of fluke on
692 DDWG (kg/head/d) calculated using IPW with DRGLM or LME model. The numbers
693 after the method on the y-axis indicate the minimum number of breeders per
694 producer for an observation to be included, as shown in Table 2. Here, the effect is
695 expressed as the advantage of an animal with no evidence of fluke over an animal
696 with an active fluke lesion.

697

698 Figure 4: Marginal estimates and 95% confidence intervals for the effect of fluke on
699 days alive (d) calculated using IPW with DRGLM or LME model. The numbers after

700 the method on the y-axis indicate the minimum number of breeders per producer for
701 an observation to be included, as explained in Table 2. Here, the effect is expressed
702 as the advantage of an animal with no evidence of fluke over an animal with an
703 active fluke lesion.

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Table 1. Parameters necessary for estimation of mean emissions intensity for the three fluke scenarios, using data from the full data set. Here unweighted average values over all steers, heifers and bulls are presented.

Parameter	Units	No fluke	Active fluke	Historic fluke	Source
Age at first calving	days	986	1025	1020	Gates (2013)
Average age at slaughter	days	684	698	703	Abattoir data (this study)
Average weight at slaughter	kg LW	659	647	654	Abattoir data (this study)
Average growth rate	kg LW/day	0.89	0.86	0.86	Abattoir data (this study)

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Table 2. Marginal effects models for the effect of Fault on DDWG and Days Alive, determined from doubly robust GLMs applied to data weighted according to the IPW in which the sets of adjustment variables included producer, breeder, year of birth, season of birth, and category for each of the selected sets of data (single breeder-producer combinations, minimum of 1 animal per producer and 1 animal per breeder, 10 animals per producer and 10 animals per breeder, through to 500 animals per breeder and 500 animals per producer). In all cases, the model used active fault as the reference level, so a positive effect estimate indicates that relative to the active fault level, animals with historic fault or no fault were assigned a higher value. Results are reported here at up to 4 significant figures for ease of comparison only. Results reported in the text are based on the model in bold.

Method	Sample	N.Obs	N.Breeders	N.Finishers	Variable	CI.95.Lo	Estimate	CI.95.Hi	P
IPW + DRGLM		500	20680	44	103 DDWG	0.014	0.032	0.050	0.00053
IPW + DRGLM		500	20680	44	103 DA	-36.13	-18.30	-0.456	0.0444
IPW + DRGLM		100	177860	819	433 DDWG	0.011	0.016	0.021	2.79×10^{-09}
IPW + DRGLM		100	177860	819	433 DA	-15.63	-10.70	-5.774	2.09×10^{-05}
IPW + DRGLM		50	213806	1217	589 DDWG	0.012	0.017	0.022	5.64×10^{-12}
IPW + DRGLM		50	213806	1217	589 DA	-15.49	-10.97	-6.459	1.91×10^{-06}
IPW + DRGLM		10	236380	1805	951 DDWG	0.011	0.016	0.021	9.06×10^{-11}
IPW + DRGLM		10	236380	1805	951 DA	-15.07	-10.52	-5.962	6.05×10^{-06}
IPW + DRGLM		1	240065	2492	1340 DDWG	0.028	0.122	0.215	0.0107
IPW + DRGLM		1	240065	2492	1340 DA	-289.4	-158.9	-28.48	0.017
IPW + DRGLM	Single breeder/producer	16665	380	513	DDWG	-0.0453	-0.002	0.041	0.925
IPW + DRGLM	Single breeder/producer	16665	380	513	DA	-43.21	-10.83	21.56	0.512
LME		500	20680	44	103 DDWG	0.003608	0.01085	0.01810	0.0033
LME		500	20680	44	103 DA	-16.45	-9.88	-3.296	0.0033
LME		50	213806	1217	589 DDWG	*NA	*NA	*NA	*NA
LME		50	213806	1217	589 DA	-13.79	-11.95	-10.10	<0.0001
LME		1	240065	2492	1340 DDWG	0.007776	0.009479	0.01118	<0.0001
LME		1	240065	2492	1340 DA	*NA	*NA	*NA	*NA
LME (Mazeri et al., 2017)	Holstein-Friesian	6197	NA	NA	DA	-31	-23	-15	NA
LME (Mazeri et al., 2017)	All breeds	169605	NA	NA	DA	-12	-10	-9	NA

Note that there are more producers/breeder because some breeders might have supplied more than one producer. CI.95.Lo – lower 95% confidence interval; CI.95.Hi – upper 95% confidence interval; DA – days alive (birth to slaughter); DDWG – daily dead-weight gain; DRGLM – doubly-robust generalized linear model; IPW – inverse probability weighting; LME – linear mixed effects; NA – data not available; * it was not possible to derive a result for the LME with breeder and producer due to false convergence

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Table 3: Summary of the effect estimates of the competing variables, category, season of birth, year of birth on DDWG and days alive, as derived from linear mixed effects model fit by REML to the full dataset of 240065 animals, with breeder and finisher as random factors.

DDWG					
Variable	Level	Estimate	SE	t-value	p-value
Category	Heifer	-0.2893	0.0009279	-311.8	< 0.0001
	Steer	-0.2470	0.0009381	-263.3	< 0.0001
Season of Birth	Spring	-0.003510	0.0003814	-9.202	< 0.0001
Year of Birth*		0.01797	0.0001544	116.4	< 0.0001
Days Alive					
Variable	Level	Estimate	SE	t-value	p-value
Category	Heifer	187.8	0.9933	189.1	< 0.0001
	Steer	205.4	1.004	204.5	< 0.0001
Season of Birth	Spring	10.55	0.4087	25.81	< 0.0001
Year of Birth*		-26.41	0.1654	-159.7	< 0.0001

REML – Restricted maximum likelihood; SE – Standard deviation.

Reference levels for variables: For category, bull; for season of birth, autumn; for year, 2011, *and note that Estimate here refers to additional effect of each year after 2011.

For all variables, 238721 degrees of freedom.

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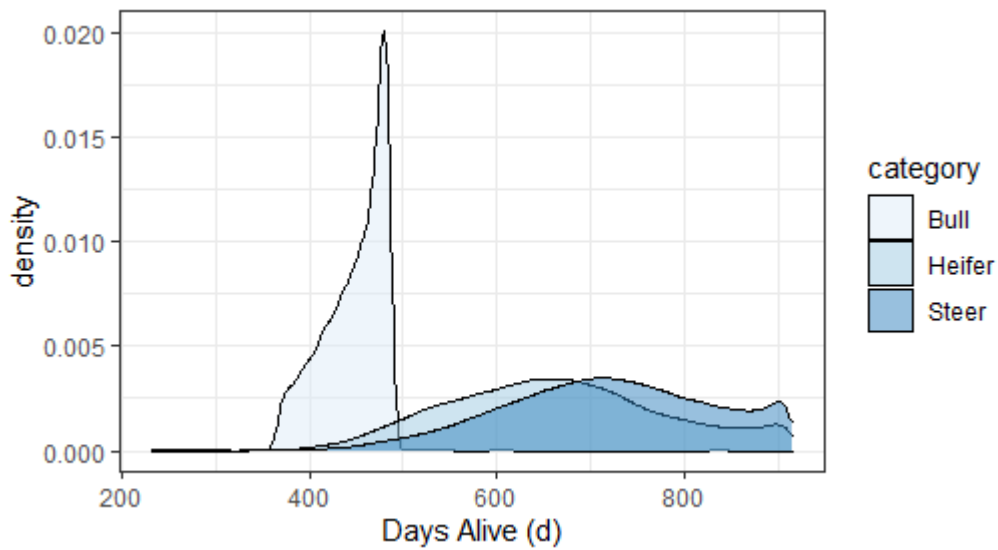
Table 4. Emissions intensity (EI) for the three fluke scenarios, estimated using SAEM

	Units	No fluke	Active fluke	Historic fluke
EI of liveweight	kg CO ₂ eq / kg LW	14.9	15.2	15.1
EI of carcass weight	kg CO ₂ eq / kg CW	25.2	25.6	25.6
Change in EI relative to no fluke			+1.5%	1.4%

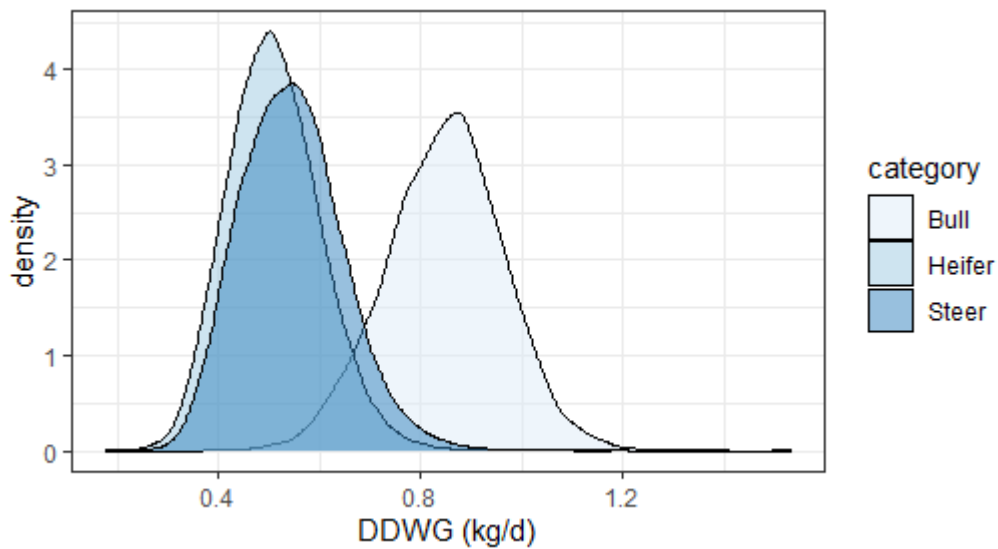
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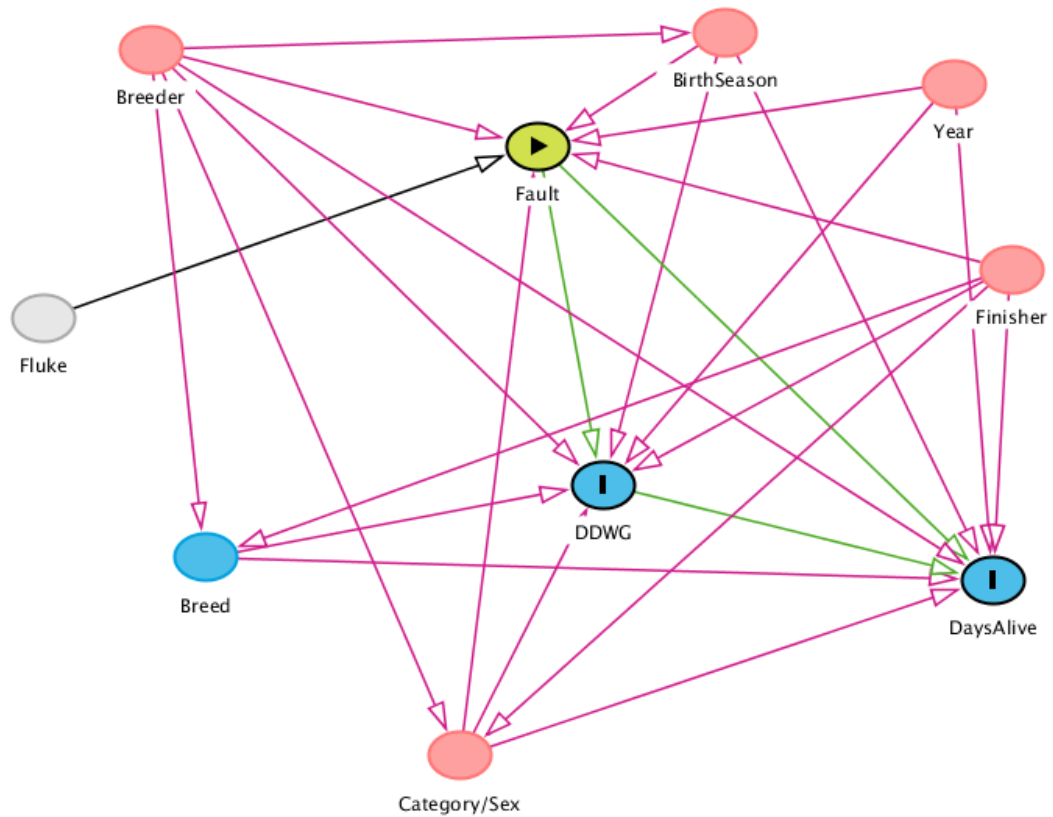


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731 Figure 1: A (top) Density plot of days alive for steers, heifers and bulls. Asymmetric
732 distributions are a consequence of abattoir buying patterns. Bulls younger than 500 d and
733 other cattle younger than 900 d receive a premium price, resulting in sharply truncated
734 distributions on these boundaries. B (bottom) Density plot of daily deadweight gain (DDWG,
735 kg/d) for steers, heifers and bulls. Growth rates in bulls in UK systems are substantially
736 higher than those of steers and heifers.

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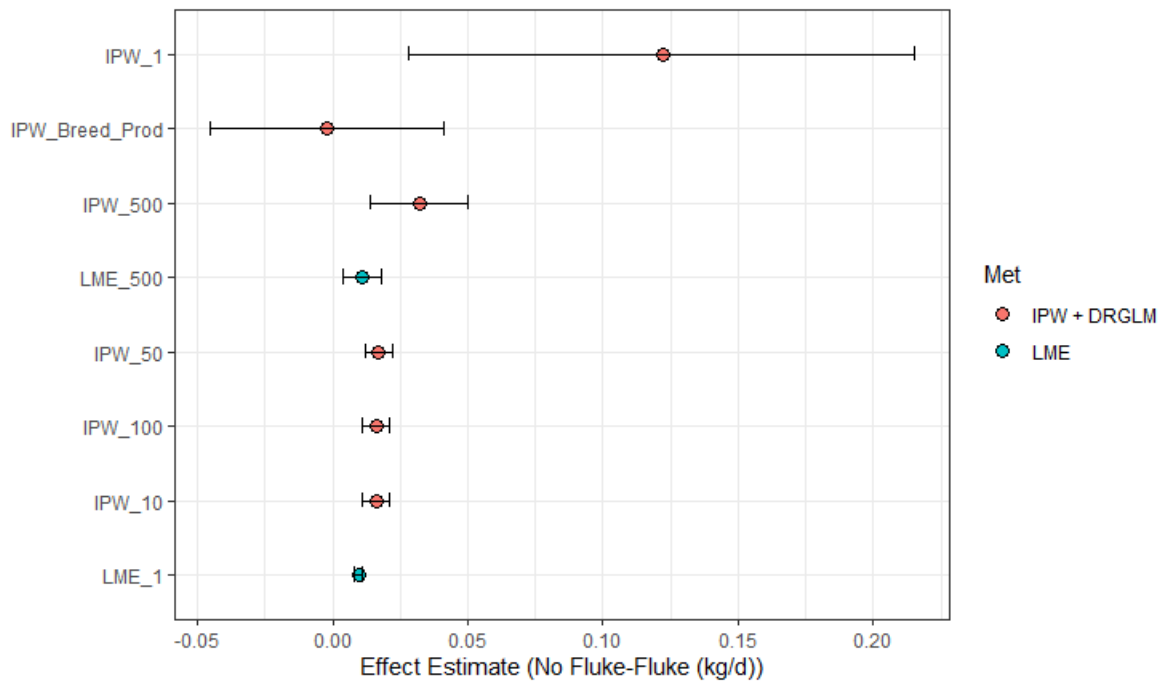
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742 Figure 2: Directed acyclic graph including the variables in the model. The green symbol with
743 triangle is the exposure variable (fault); blue symbols with "I" are the outcome variables of
744 days alive and daily dead-weight gain (DDWG); blue symbols without "I" are ancestors of the
745 outcome variables (therefore, competing variables); pink symbols are potential confounders
746 (ancestors of the exposure variable and the outcome variables). Grey symbols are
747 unobserved variables. Green edges are causal paths and pink edges are biasing paths. Here
748 fluke represents the true state of fluke exposure and we are using the observed variable of
749 fault as proxy for exposure to the true fluke state.

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Figure 3: Marginal estimates and 95% confidence intervals for the effect of fluke on

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DDWG (kg/head/d) calculated using IPW with DRGLM or LME model. The numbers

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after the method on the y-axis indicate the minimum number of breeders per

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producer for an observation to be included, as explained in Table 2. Here, the effect

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is expressed as the advantage of an animal with no evidence of fluke over an animal

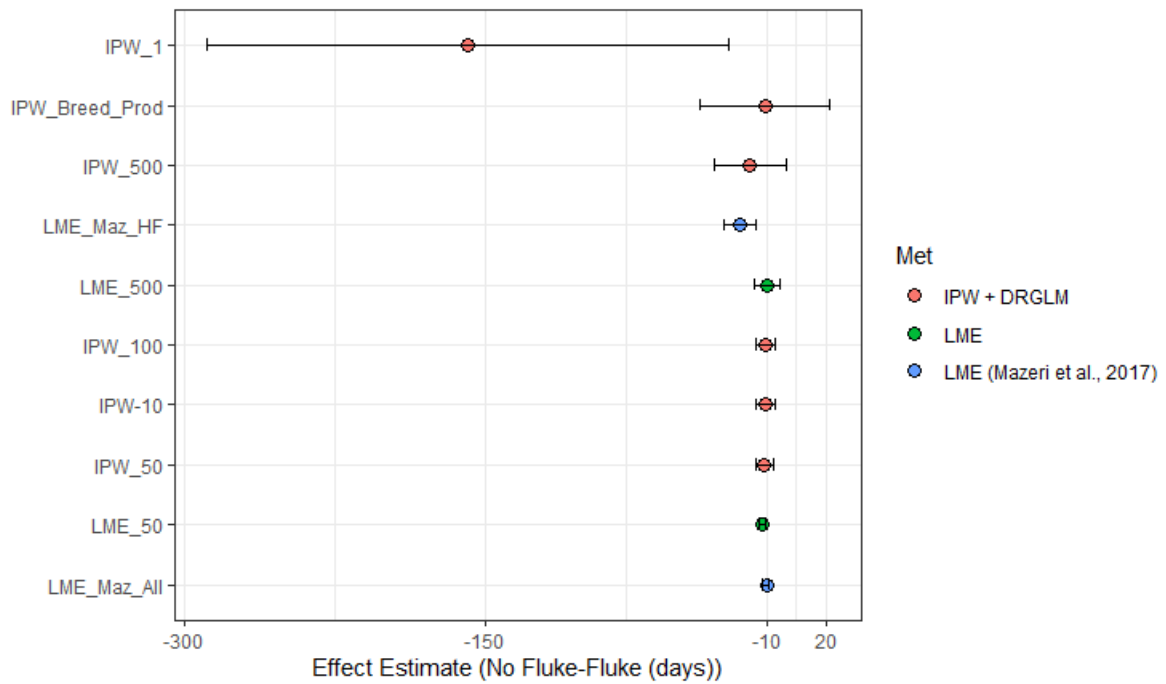
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with an active fluke lesion.

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768 Figure 4: Marginal estimates and 95% confidence intervals for the effect of fluke on
769 days alive (d) calculated using IPW with DRGLM or LME model. The numbers after
770 the method on the y-axis indicate the minimum number of breeders per producer for
771 an observation to be included, as explained in Table 2. Here, the effect is expressed
772 as the advantage of an animal with no evidence of fluke over an animal with an
773 active fluke lesion.

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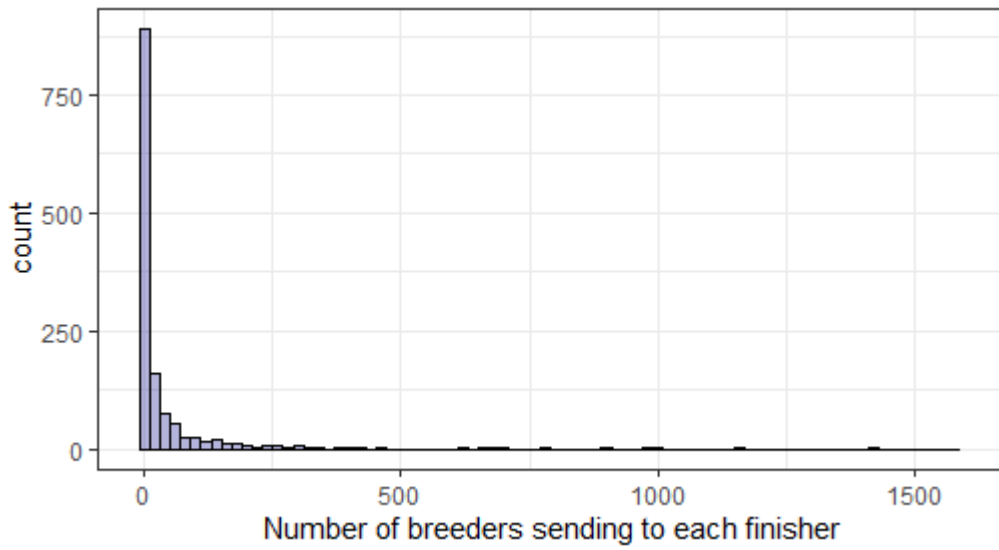
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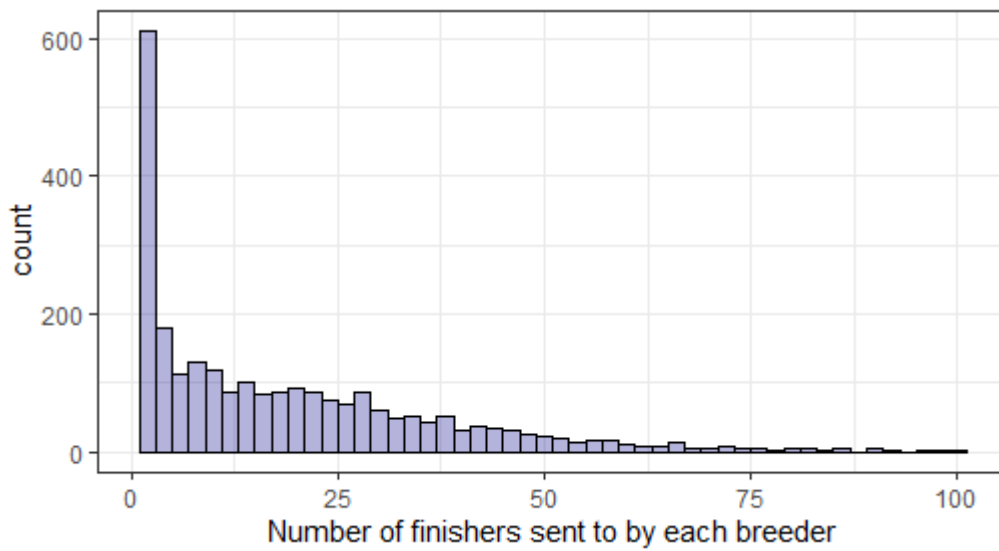
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778 **Supplementary material**

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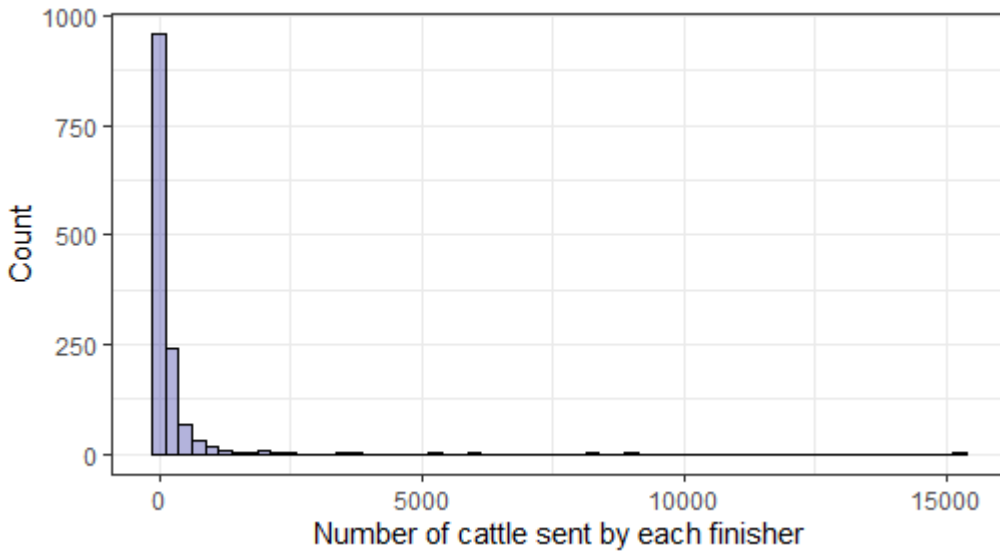
783 Figure S1. Histograms of the number of breeders supplying cattle to each finisher

784 (top) and the number of finishers to whom each breeder's animals are supplied

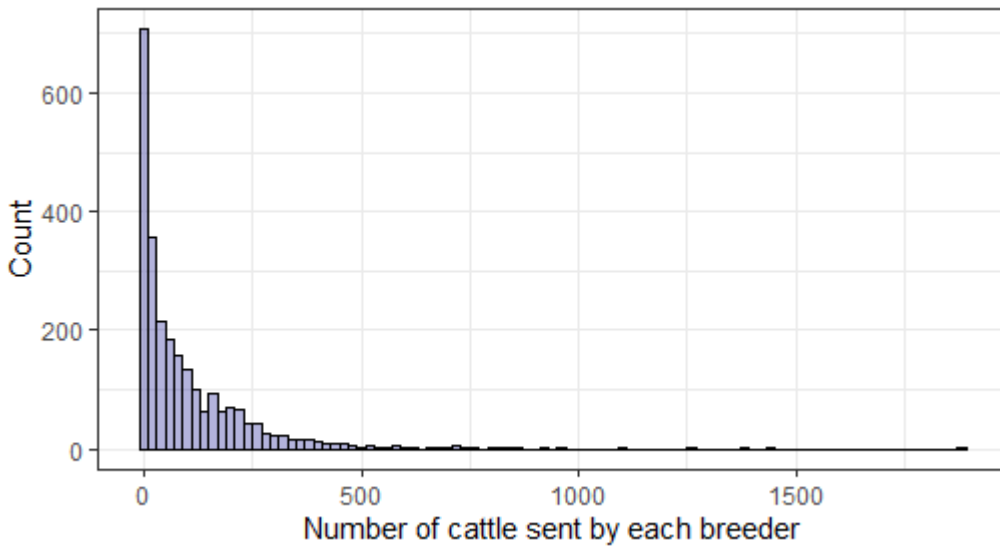
785 (bottom).

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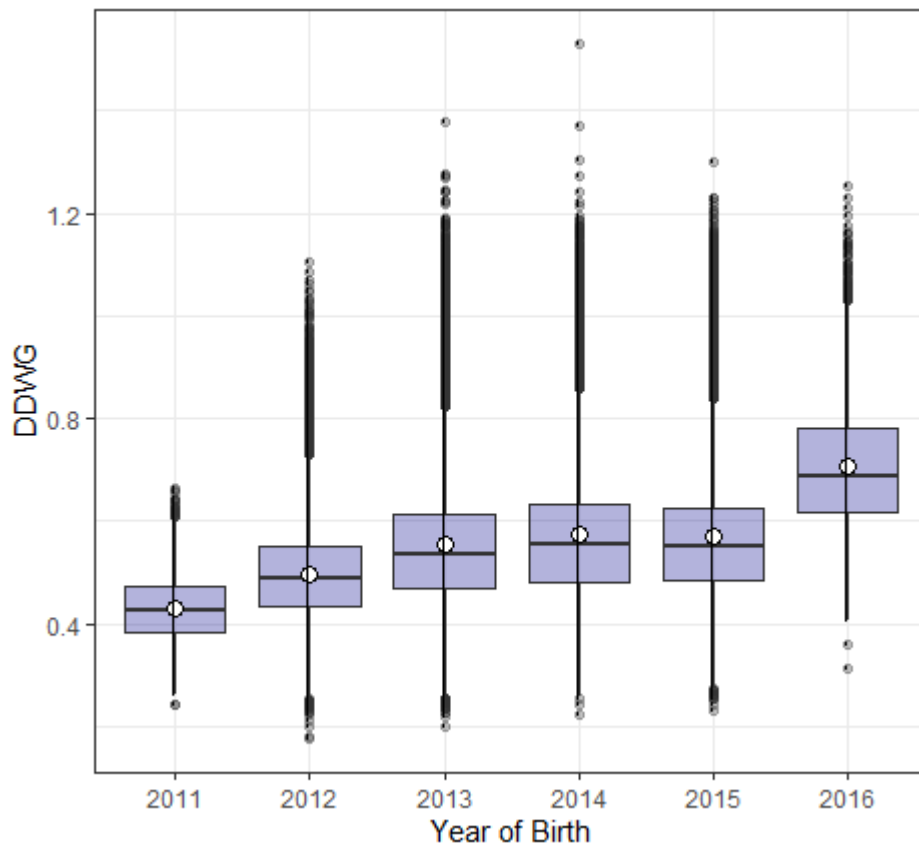
791 Figure S2: Histograms showing the number of animals sent to slaughter by each

792 finisher (top) and by each breeder (bottom).

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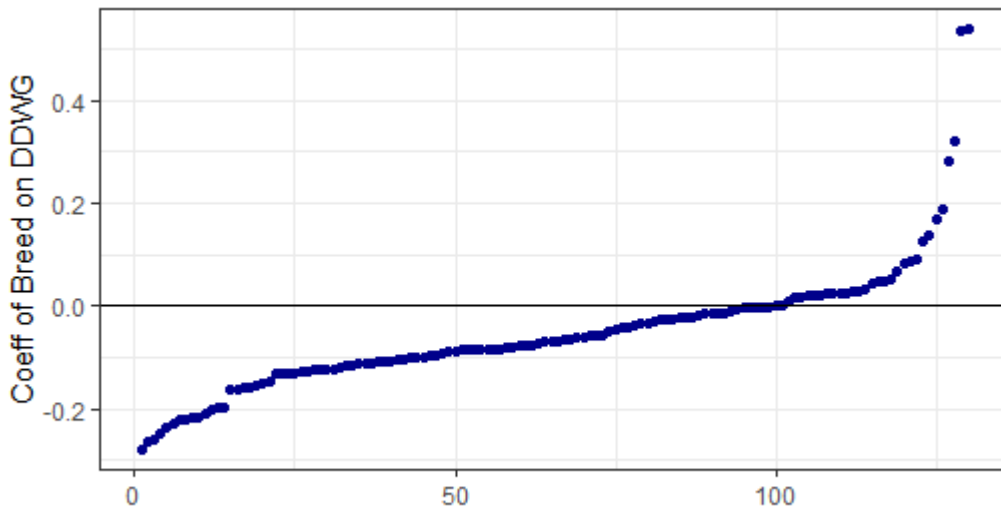
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797 Figure S3. Box and whisker plot of daily dead-weight gain (DDWG) by year of birth,
798 from the full dataset of 240065 animals and without separation of bulls, heifers and
799 steers. Horizontal bar in box is median; white circle is mean.

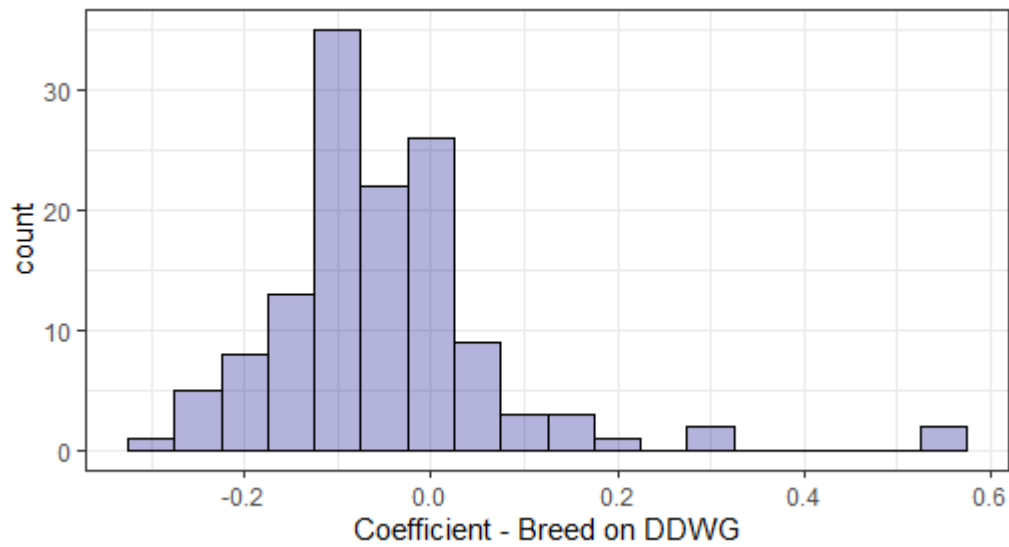
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806 Figure S4. Effect of 129 breeds on daily dead-weight gain (DDWG in kg/d): Upper figure

807 shows the ranked coefficients of breed on DDWG and lower figure shows a histogram of the

808 coefficients. (Chi-squared test of frequencies for breed and fault: X-squared = 1113.5, df =

809 258, p-value < 2.2e-16)

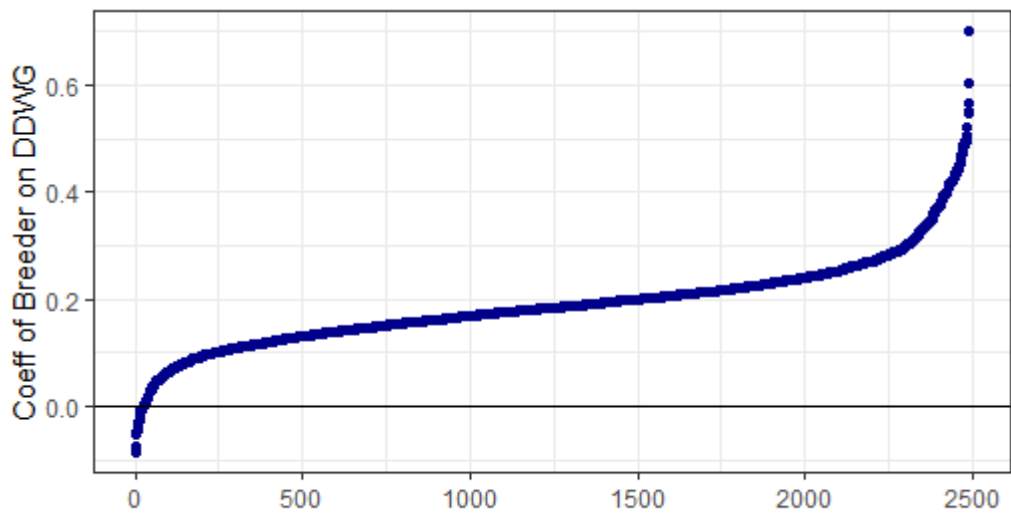
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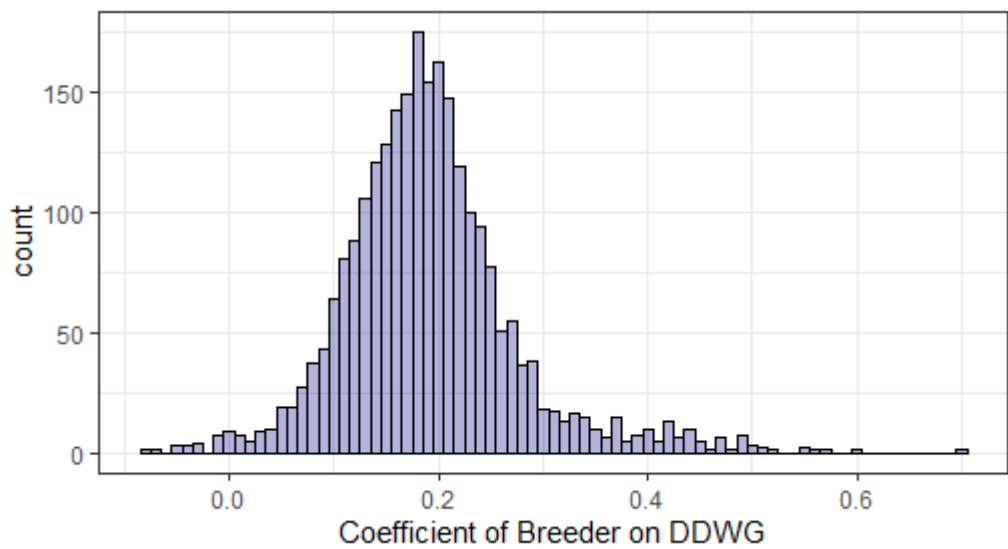
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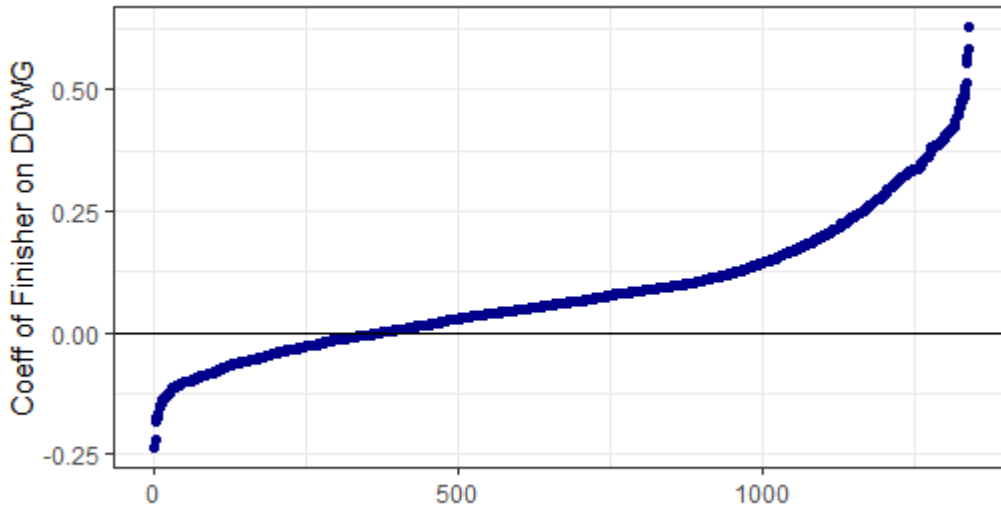
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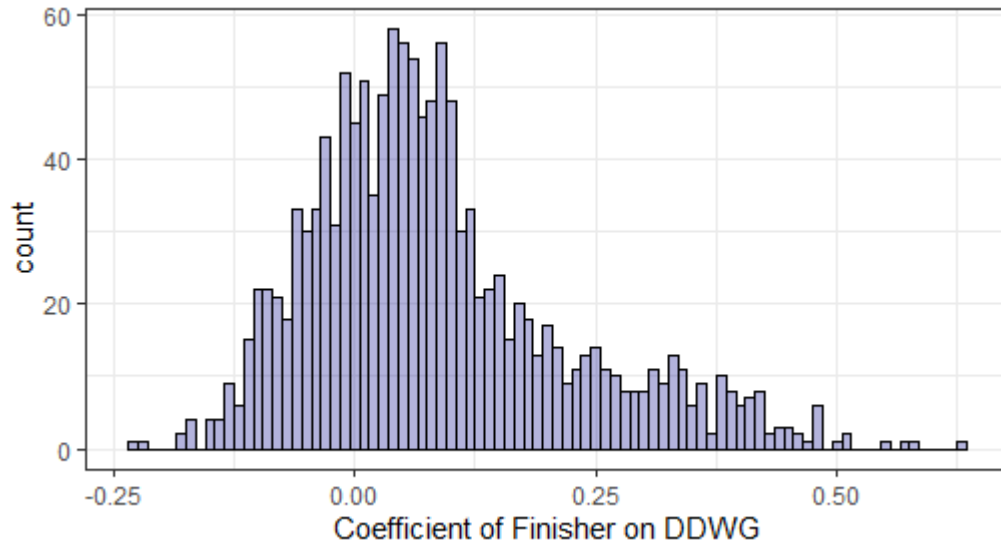
818 Figure S5: Upper figure shows the ranked coefficients of breeder on DDWG and lower

819 figure shows a histogram of the coefficients.

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825 Figure S6: Upper figure shows the ranked coefficients of finisher on DDWG

826 (kg/head/d) and lower figure shows a histogram of the coefficients.

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