Statistical analysis of precapillary sphincter pulsatility data

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The pulsatility data consisted of fast measurements of diameter and center point for the same mice. These measurements were Fourier-transformed, and the harmonics of the transformed data were interpreted as representing the pulsatility of the measured quantities.

Questions

We aimed to answer the following questions:

Question 0.1. *Do diameter or centre pulsatility depend on age? If so, is this dependency mediated by the higher average blood pressure of adult mice compared with old mice?*

Question 0.2. *Does sphincter ablation affect diameter and/or centre pulsatility differently in adult and old mice?*

Question 0.3. *How does blood pressure affect diameter and centre pulsatility?*

Question 0.4. *Do hypertension and sphincter ablation influence diameters, Pd, and Pc differently for different vessels?*

To answer these questions we created a pulsatility dataset and fit a series of statistical models to it.

Description of the dataset

We used the first harmonic of each transformed time series as a dependent variable. It might have been preferable to aggregate all the available power harmonics, but this would have complicated our measurement model, and in any case power at the subsequent harmonics was typically negligible compared with the first.

For each measurement the following information was available:

- the identity of the mouse, and that mouse's age (adult or old)
- the vessel type (penetrating artery, bulb and first three capillary orders)
- the treatment (baseline, after hypertension and after ablation)
- the mouse's blood pressure, measured at the femoral artery

The final dataset included 514 joint measurements of diameter and centre pulsatility, calculated as described above. These measurements are shown in Figure 1.

Figure 2 shows the relationship between pressure and the measurements in our dataset for both age categories. The light dots show raw measurements and the darker dots show averages within evenly sized bins.

Figure 3 shows the relationship between diameter and the measurements in our dataset for all vessel type categories. The light dots show raw measurements and the darker dots show averages

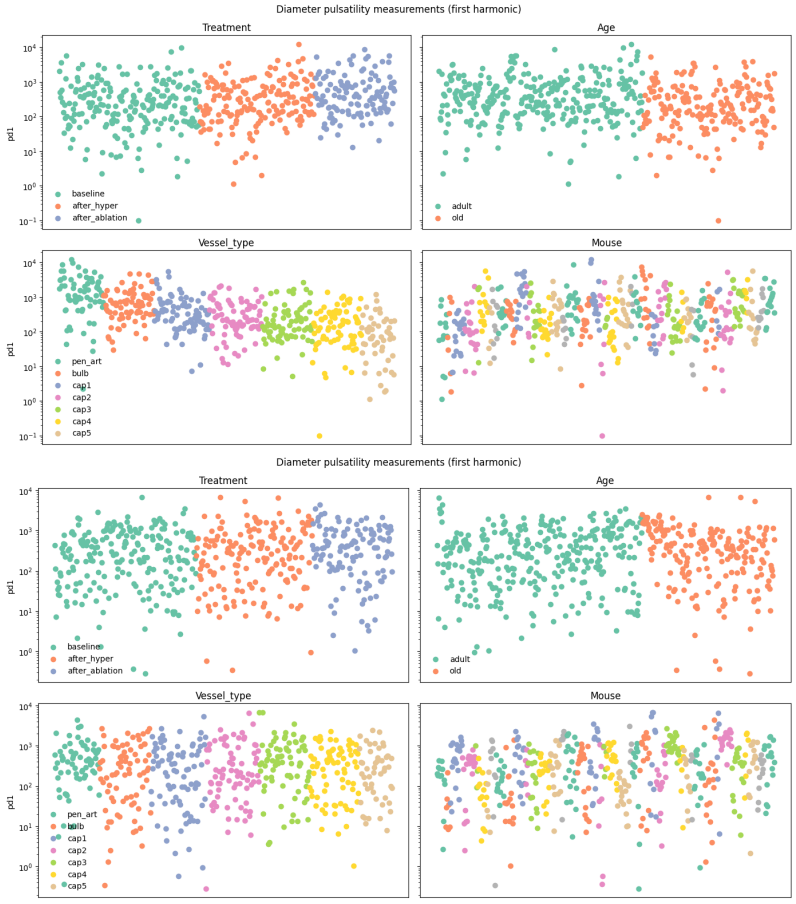

Figure 1: The modelled measurements, shown in order of the coloured categories.

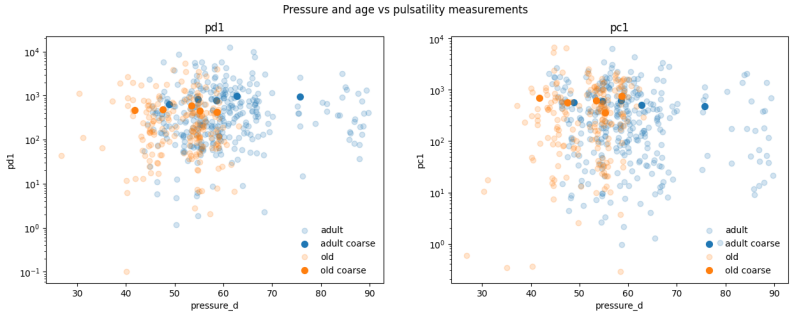

Figure 2: Pulsatility measurements plotted against the corresponding pressure measurements and coloured according to age. Darker dots indicate averages within evenly sized pressure bins.

within evenly sized bins. There is a clear positive relationship between measured absolute diameter and diameter pulsatility, and it is approximately the same for all vessel types.

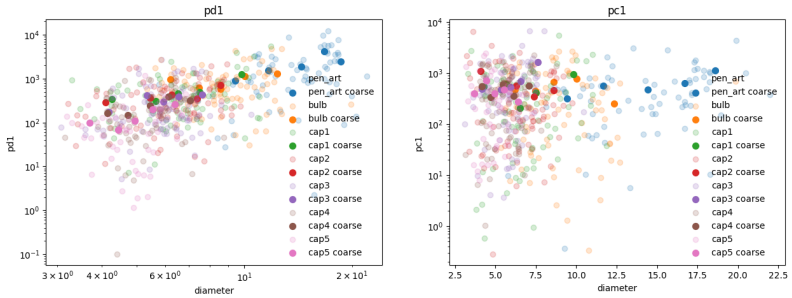

Figure 3: Pulsatility measurements plotted against the corresponding diameter measurements and coloured according to vessel type. Darker dots indicate averages within evenly sized pressure bins.

Missing data

Data from one mouse (index 310321) were excluded after some extreme measurements were observed:

310321 is a mouse where we did not see any whisker response, it reacted to angiotensin II, but the BP increase was abrupted

for a short while and then re-established. Perhaps due to a clot or a bubble in the venous catheter. This resulted in a biphasic and slow BP increase

As with the whisker stimulation data we assumed that all absent measurements were missing at random.

Statistical model

We knew from prior studies that the power harmonics should individually follow exponential distributions [REFERENCE FOR THIS]. This consideration motivated the use of exponential generalised linear models for both the centre and diameter pulsatility measurements. In this model, given measurement y and linear predictor η the measurement probability density is given by this equation:

$$p(y \mid \eta) = Exponential(y, \lambda) = \lambda e^{-\lambda y} \tag{1}$$

$$\ln \frac{1}{\lambda} = \eta \tag{2}$$

The log link function (2) was chosen so that linear changes in the term η induce multiplicative changes in the mean $\frac{1}{\lambda}$ of the measurement distribution, as we believed the effects we wanted to model would be multiplicative.

We compared four different ways of parameterising η based on the information available about a given measurement, corresponding to three hypotheses about the way the data were generated.

The simplest, or "basic", model postulates that the linear predictors η_d^{basic} and η_c^{basic} are the sums of these random variables:

$$\begin{aligned}\eta_{d,n}^{basic} &= \mu_{d,age(mouse(n))} + \alpha_{d,treatment(n)}^{treatment} + \alpha_{d,vessel\ type(n)}^{vessel\ type} \\ &\quad + \beta_d^{diameter} \cdot diameter(n) \\ \eta_{c,n}^{basic} &= \mu_{c,age(mouse(n))} + \alpha_{c,treatment(n)}^{treatment} + \alpha_{c,vessel\ type(n)}^{vessel\ type} \\ &\quad + \beta_c^{diameter} \cdot diameter(n)\end{aligned} \tag{3}$$

The basic model provided a plausible baseline against which to compare the other models.

The "interaction" model was developed to explore whether there were any important interaction effects that the basic model does not consider. For example, question b) can be interpreted as asking whether there is are any significant effects corresponding to the interaction between age and treatment. Our interaction model calculates the value of the linear predictors $\eta_d^{interaction}$ and $\eta_c^{interaction}$ as depending on age-treatment and age-treatment-vessel type interaction effects as follows:

$$\begin{aligned}\eta_{d,n}^{interaction} &= \mu_{d,age(mouse(n))} + \alpha_{d,treatment(n)}^{treatment} + \alpha_{d,vessel\ type(n)}^{vessel\ type} \\ &\quad + \alpha_{d,age(mouse(n)),treatment(n)}^{age:treatment} \\ &\quad + \alpha_{d,age(mouse(n)),treatment(n),vessel\ type(n)}^{age:treatment:vessel\ type} \\ &\quad + \beta_d^{diameter} \cdot diameter(n) \\ \eta_{c,n}^{interaction} &= \mu_{c,age(mouse(n))} + \alpha_{c,treatment(n)}^{treatment} + \alpha_{c,vessel\ type(n)}^{vessel\ type} \\ &\quad + \alpha_{c,age(mouse(n)),treatment(n)}^{age:treatment} \\ &\quad + \alpha_{c,age(mouse(n)),treatment(n),vessel\ type(n)}^{age:treatment:vessel\ type} \\ &\quad + \beta_c^{diameter} \cdot diameter(n)\end{aligned} \tag{4}$$

Next, we constructed a model that adds to the basic model parameters that aim to capture possible effects corresponding to the blood pressure measurements. To compensate for collinearity between age and pressure, our "pressure" model does not use the observed pressure as a predictor, but rather the age-normalised pressure, calculated by subtracting the mean for

each age category from the observed pressure measurement. The model for the linear predictors $\eta_d^{pressure}$ and $\eta_c^{pressure}$ is then as follows:

$$\begin{aligned}
\eta_{d,n}^{pressure} &= \mu_{d,age(mouse(n))} + \alpha_{d,treatment(n)}^{treatment} + \alpha_{d,vessel\ type(n)}^{vessel\ type} \\
&\quad + \beta_d^{diameter} \cdot diameter(n) \\
&\quad + \beta_{d,age(mouse(n))}^{pressure} \cdot norm\ pressure_n \\
\eta_{c,n}^{pressure} &= \mu_{c,age(mouse(n))} + \alpha_{c,treatment(n)}^{treatment} + \alpha_{c,vessel\ type(n)}^{vessel\ type} \\
&\quad + \beta_c^{diameter} \cdot diameter(n) \\
&\quad + \beta_{c,age(mouse(n))}^{pressure} \cdot norm\ pressure_n
\end{aligned} \tag{5}$$

Finally, we made a model that includes a pressure effect but no age-specific parameters from the pressure model. This is to test whether any age effects are due to the collinearity between age and pressure. The pressure-no-age model's linear predictors $\eta_d^{pressure\ no\ age}$ and $\eta_c^{pressure\ no\ age}$ are calculated as shown in equation (6). Note that, unlike in equation (5), the μ and $\beta^{pressure}$ parameters in equation (6) have no age indexes.

$$\begin{aligned}
\eta_{d,n}^{pressure\ no\ age} &= \mu_d + \alpha_{d,treatment(n)}^{treatment} + \alpha_{d,vessel\ type(n)}^{vessel\ type} \\
&\quad + \beta_d^{diameter} \cdot diameter(n) \\
&\quad + \beta_d^{pressure} \cdot norm\ pressure_n \\
\eta_{c,n}^{pressure\ no\ age} &= \mu_c + \alpha_{c,treatment(n)}^{treatment} + \alpha_{c,vessel\ type(n)}^{vessel\ type} \\
&\quad + \beta_c^{diameter} \cdot diameter(n) \\
&\quad + \beta_c^{pressure} \cdot norm\ pressure_n
\end{aligned} \tag{6}$$

In all of our models the α parameters were given independent, semi-informative, hierarchical prior distributions to allow for appropriate information sharing. The $\beta^{pressure}$ parameters were given independent, semi-informative, non-hierarchical prior distributions.

Results

We estimated the leave-one-out log predictive density for each model using the method described in Vehtari, Gelman, and Gabry (2017) and implemented in Kumar et al. (2019). The results of the comparison are shown below in Figure 4.

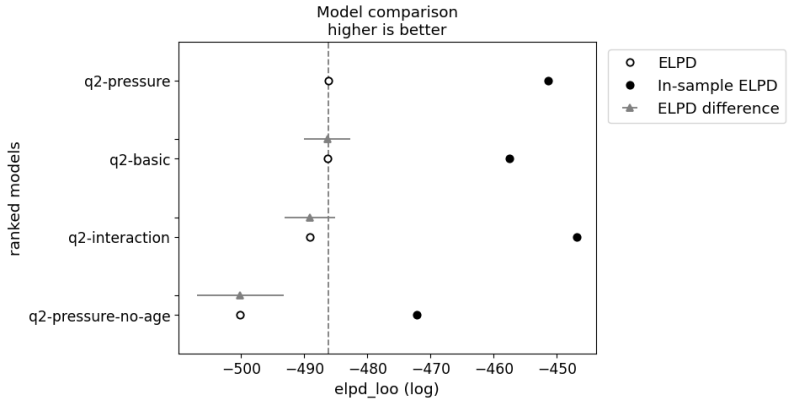

Figure 4: Comparison of estimated leave-one-out log predictive density (ELPD) for our pulsatility models. The main result is that the pressure-no-age and interaction models are clearly worse than the pressure model, as shown by the separation of the relevant grey and dotted lines.

We evaluated our models' fit to data using prior and posterior predictive checking, with the results for the pressure model shown in Figure 5.

Inspecting of the interaction model output showed that none of the interaction effect parameters that differed substantially from zero, as can be seen in Figure 6.

From this result, together with the worse estimated out of sample predictive performance as shown in Figure 4, we concluded that there were no important interaction effects, so that we could essentially discard the interaction model.

Figure 7 shows the marginal posterior distributions for other effect parameters in all three models. Note that the parameters `b_diameter` are strongly positive for diameter pulsatility in all

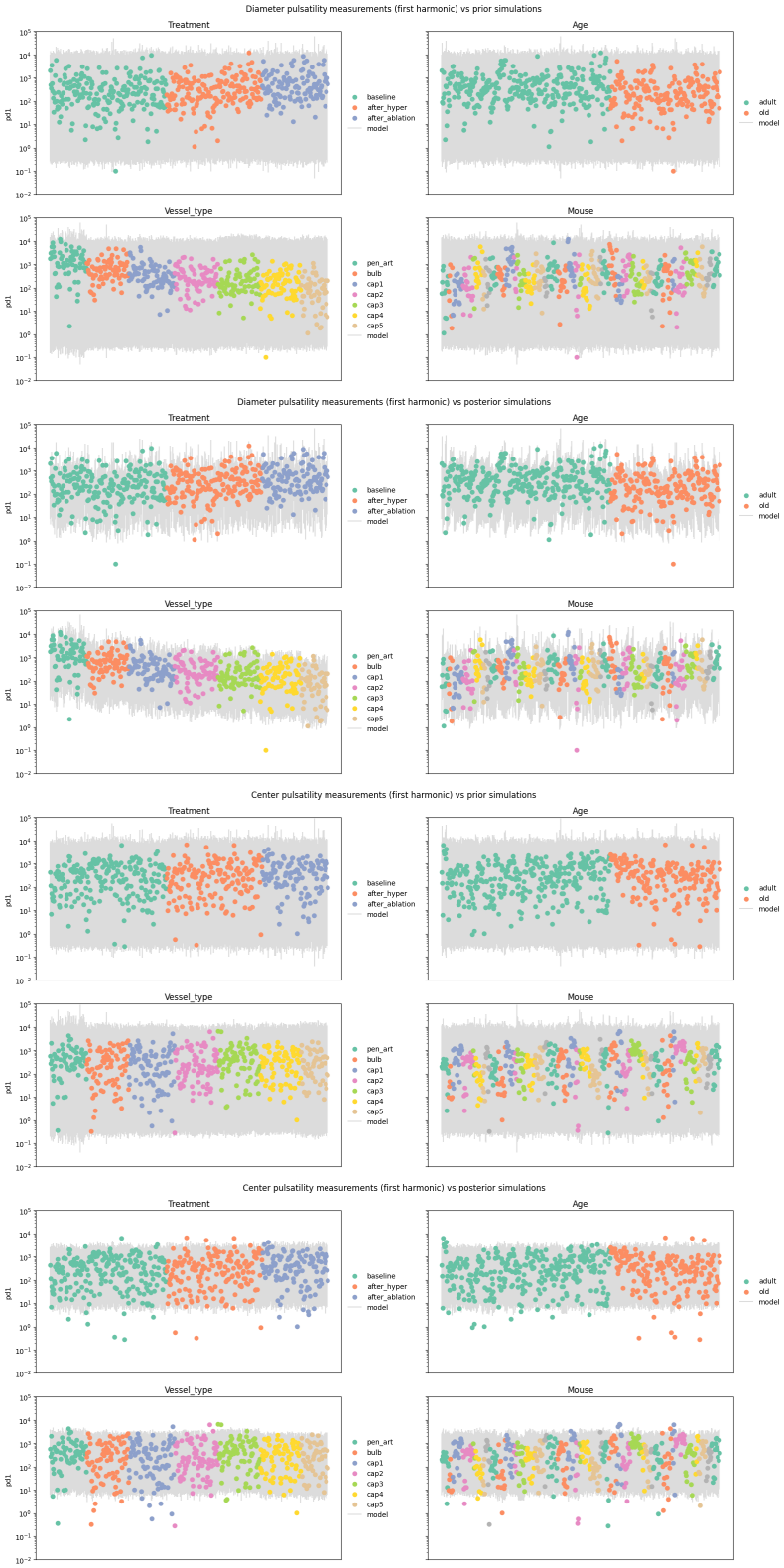

Figure 5: Prior and posterior predictive checks for the pressure model.

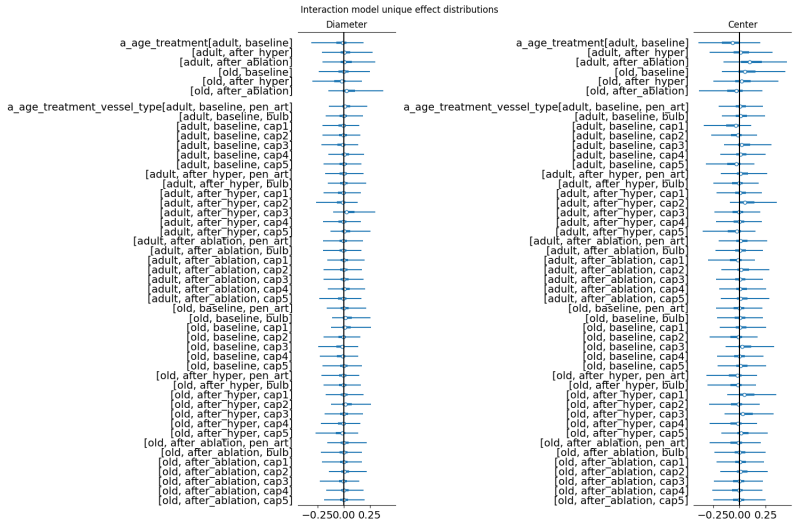

Figure 6: Marginal posterior quantiles for the unique effects in the interaction model.

models and also mostly positive for centre pulsatility. There is also a strong trend for diameter pulsatility to decrease with the order of the vessel and no particular vessel type trend for centre pulsatility.

Answers to specific questions

To address Question 0.1, i.e. whether there are important age effects, Figure 8 plots the distribution of age effect differences (adult minus old) for each measurement type in the pressure model.

This graph shows that, in this model, the mean parameter for diameter pulsatility in adult mice was higher than for old mice in every single posterior sample: in other words there is a clear trend for older mice to have lower diameter pulsatility. There is a smaller opposite trend for centre pulsatility measurements, but it is not clearly separated from zero, indicating that the direction of the effect is not fully settled.

Question 0.2 is whether the age effects are explained by the generally higher blood pressure of the adult mice. This is mostly

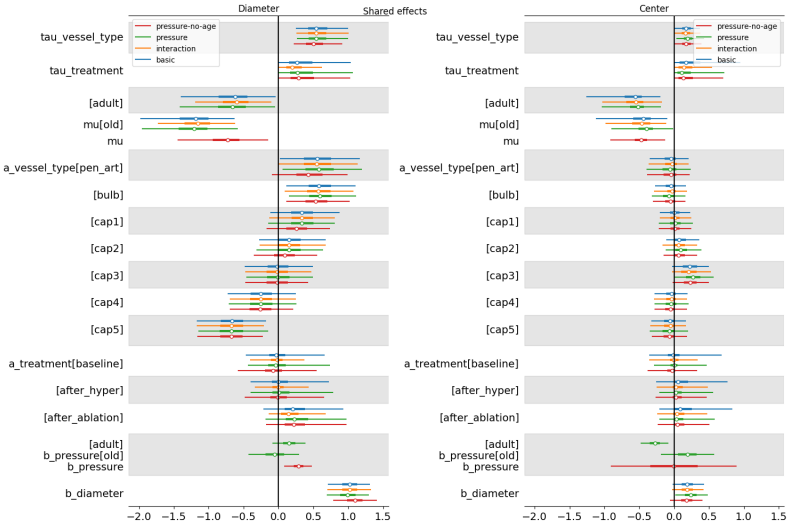

Figure 7: Marginal posterior quantiles for shared model effects.

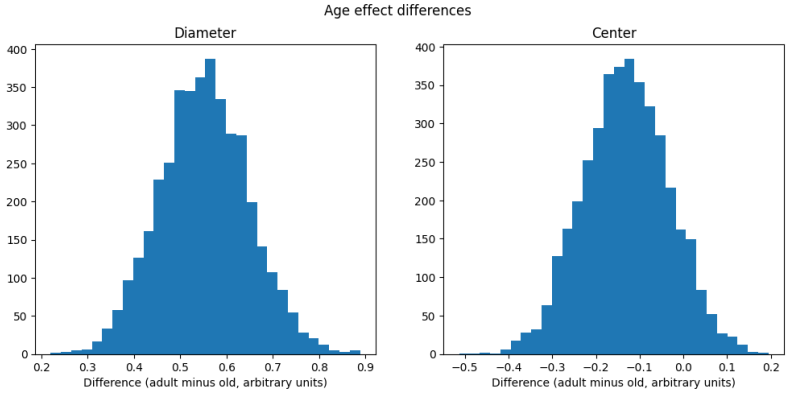

Figure 8: Posterior distribution of age effect differences for each measurement type.

answered by the poorer estimated out of sample predictive performance of the pressure-no-age model compared with the other models as shown in Figure 4. This shows that there is information in the age labels beyond what is contained in the pressure measurements. It is nonetheless possible that different pressure explains the difference between old and adult mice, but that the pressure measurements did not reflect the true pressure at the measured vessels. This is plausible since the pressure measurements were taken at a different location.

Figure 9 shows the difference in $\beta^{pressure}$ parameters for old and adult mice in the pressure model in order to answer Question 0.3. This shows a weak tendency of the pressure effect on diameter pulsatility to be more positive for adult mice than for old mice, and a strong opposite tendency for centre pulsatility. Taking the absolute values into account, the analysis suggests that greater measured pressure is not strongly related to diameter pulsatility and correlates with reduced centre pulsatility for adult mice but not for old mice.

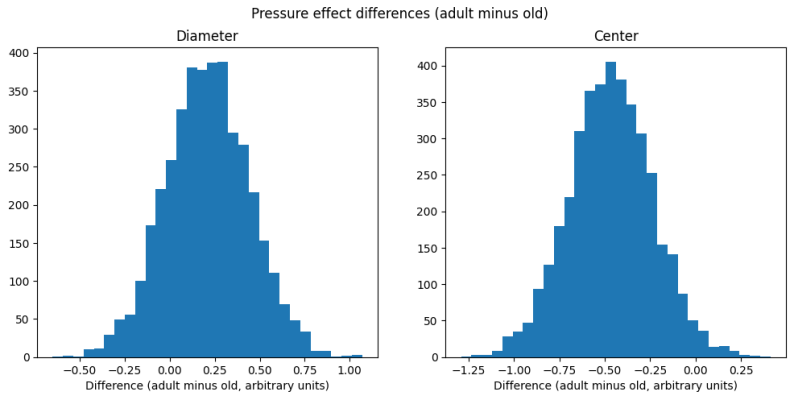

Figure 9: Posterior distribution of pressure effect differences for each measurement type.

To illustrate the effect of treatments, and specifically sphincter ablation relative to hypertension (i.e. to answer Question 0.4) Figure 10 shows the difference between the effect for each treatment and the baseline treatment effect. There is a clear effect of ablation to increase diameter pulsatility and no clear effects of hypertension on diameter pulsatility or of either treatment on centre pulsatility.

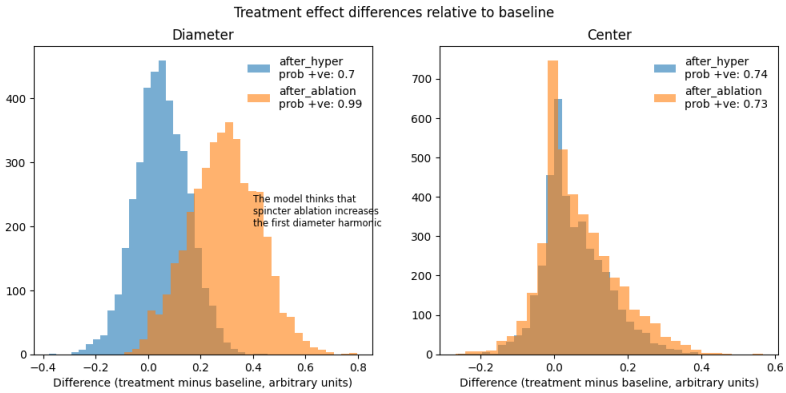

Figure 10: Posterior distribution of treatment effect differences for each measurement type.

Kumar, Ravin, Colin Carroll, Ari Hartikainen, and Osvaldo Martin. 2019. "ArviZ a Unified Library for Exploratory Analysis of Bayesian Models in Python." *Journal of Open Source Software* 4 (33): 1143. https://doi.org/10.21105/joss.01143.

Vehtari, Aki, Andrew Gelman, and Jonah Gabry. 2017. "Practical Bayesian Model Evaluation Using Leave-One-Out Cross-Validation and WAIC." *Statistics and Computing* 27 (5): 1413–32. https://doi.org/10.1007/s11222-016-9696-4.