On the Relationship between Treatment Effect Heterogeneity and the Variability Ratio Effect Size Statistic

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1 Abstract

Recently, the variability ratio (VR) effect size statistic has been used with increasing frequency in the study of differences in variation of a measured variable between two study populations. More specifically, the VR effect size statistic allows for the detection of treatment effect heterogeneity (TEH) of medical interventions. While a VR that is different from 1 is widely acknowledged to implicate a treatment effect heterogeneity (TEH) the exact relationship between those two quantities has not been discussed in detail thus far.

In this note we derive a precise connection between TEH and VR. In particular, we derive precise upper and lower bounds on the TEH in terms of VR. Moreover, we provide an exemplary simulation for which VR is equal to 1 and there exist TEH.

Our result has implications for the interpretation of VR effect size estimates regarding its connection to treatment effect heterogeneity of (medical) interventions.

Keywords — variability ratio, treatment effect heterogeneity, causal inference

2 Introduction

Recently, the variability ratio (VR) effect size statistic (defined in Hedges and Nowell (1995), and proposed in Nakagawa et al. (2015)) has been used in various meta-analyses to investigate the difference of the total amount of variance present between two experimental groups.

Senior et al. (2016) compared the effects of two dietary interventions on variability in weight. Winkelbeiner et al. (2019), McCutcheon et al. (2019) and Mizuno et al. (2020) studied the variability of antipsychotic drug response in schizophrenia. Plöderl and Hengartner (2019), Maslej et al. (2020) and Volkmann, Volkmann, and Mueller (2020) investigated the variability of antidepressants’ response in depression.

Other recent works that have used the VR effect size statistic in order to compare the variability between two groups include Brugger and Howes (2017), Pillinger et al. (2019), Rogdaki et al. (2020) as well as Brugger et al. (2020).

While a VR that is different from 1 is widely acknowledged to implicate a variation in treatment effect the exact relationship between those two quantities has not discussed in detail thus far.

The purpose of this note is to derive a precise connection between the TEH and the VR. Moreover, we provide an exemplary simulation for which VR is equal to 1, yet there exist substantial TEH.

3 Methods – Individual treatment effect

The treatment effect of individual \( i \) with respect to a given (medical) treatment is defined as (cf. e.g. Morgan and Winship (2015)),

\[
\delta_i = Y_{i}^{1} - Y_{i}^{0},
\]

where \( Y_{i}^{a} \) denotes the potential outcome of individual \( i \) with respect to treatment \( a \in \{0, 1\} \). The potential outcome \( Y_{i}^{a} \) represents the outcome that the individual \( i \) would have had, had the individual \( i \) received the treatment \( a \), irrespective of the factual treatment, the treatment that actually was received by the individual. The fundamental problem of causal inference (see Holland (1986)), states that we can never observe both \( Y_{i}^{1} \) and \( Y_{i}^{0} \) at the same time. Moreover, the notation reflects the fact that we make the Stable Unit Treatment Value Assumption (SUTVA) assumption, which allows us to write the potential outcomes for an individual \( i \) as a function of the individual’s own

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Abbreviations: VR, variability ratio; TEH, treatment effect heterogeneity
treatment assignment alone, rather than the treatment assignment of all individuals in the population. Mathematically, \( Y_{t_i}^a \), \( Y_{t_i}^1 \) of size \( N \) as a random sample from an infinite population. More formally, we consider \( Y_{t_i}^a \) to be realizations of a population level random variable \( Y^a \). Similarly, \( \delta_i \) are realizations of a population level random variable \( \delta \).

In summary, there are two levels of randomness that we consider. Firstly, we randomly draw individuals \( i = 1, \ldots, N \) from an infinite population, each individual having an associated pair \(( Y_{t_i}^0, Y_{t_i}^1 \) of potential outcomes. Secondly, a predetermined number \(( 0 < N_1 < N )\) of individuals get randomly assigned to treatment \( (a = 1) \), the remaining \(( N_0 = N - N_1 )\) individuals get assigned to the control \( (a = 0) \) group, and the associated outcomes \( Y_i = Y^a \) are observed. The uncertainty in any type of estimate that results from these two levels of randomness may be referred to as sampling-based and design-based uncertainty, respectively (see Abadie et al. (2020)).

Notably, there is an additional layer of randomness that might be considered. We could assume that for each individual \( i \), \( Y_{t_i}^a \) are random variables rather than mere realizations of a population level random variable \( Y^a \). In this case one might refer to \( \delta_i \) as the random treatment effect of the individual \( i \). Realizations \( y_{t_i}^a \) of \( Y_{t_i}^a \) could be viewed as draws from a "metaphorical population", comprising the possible eventualities that might have occurred but mainly didn’t (see Spiegelhalter (2019)). Alternatively, the source for this part of the randomness could be a model for measurement error, epistemological uncertainty, or could reflect the assumption that the individual \( i \) has a truly random outcome.

3.1 Treatment effect heterogeneity

Treatment effect heterogeneity (TEH) is present if not all individuals have the same individual treatment effect, i.e. \( \delta_i \) is not the same for all individuals. In the language of the super-population perspective this means that \( \text{Var}(\delta) > 0 \). Of course, in any practical situation it is impossible not to have TEH. The more interesting question to study is the question about the degree or the magnitude of TEH. It can be quantified by estimating the magnitude of \( \text{Var}(\delta) \) or by identifying a relevant (w.r.t. the application at hand) subgroup \( X \) of the population for which \( E[\delta|X] - E[\delta] \) is large.

In the case of random individual treatment effect, we need to distinguish between inter- and intra-individual TEH. The inter-individual TEH could be defined as the variation between individuals of the average random individual treatment effect \( (E[\delta_i]) \).

3.2 Variability Ratio

We define the variability ratio \( \nu \) (cf. Hedges and Nowell (1995)) as
\[
\nu = \frac{\sigma_1}{\sigma_0}
\]
where \( \sigma_0^2 = \text{Var}(Y^0) \), for \( a = 0, 1 \), are the super-population variances.

In the case of sufficiently large sample sizes \( N_0, N_1 \), sufficiently large values \( \sigma_a \) and (approximately) normally distributed \( \ln \sigma_a \), an unbiased estimator of \( \ln \nu \) and its sample variance (cf. Raudenbush and Bryk (1987); Nakagawa et al. (2015)) are given by
\[
\ln VR = \ln \left( \frac{s_1}{s_0} \right) + \frac{1}{2(N_1 - 1)} - \frac{1}{2(N_0 - 1)}
\]
\[
s^2_{\ln VR} = \frac{1}{2(N_1 - 1)} - \frac{1}{2(N_0 - 1)}.
\]
Here, \( s_0 \) and \( s_1 \) denote the finite sample variances of treatment and control units’ observed scores \( Y_i \).

4 Results – Treatment effect heterogeneity and variability ratio

In order to derive the main analytical relationship between TEH and the VR effect size statistic we consider two time points \( t = 0 \) (baseline) and \( t = 1 \) (endpoint). We denote by \( Y_{i0}^a \) the potential outcomes of individual \( i \) at time \( t \) with respect to the treatment \( a \). We assume that \( Y_{i0}^0 \equiv Y_{i0}^1 \), i.e. there is no effect at baseline. Then, we may write
\[
Y_{i1}^a = Y_{i0}^a + (Y_{i1}^0 - Y_{i0}^a) + a \cdot (Y_{i1}^1 - Y_{i0}^a)
\]
\[
= Y_{i0}^0 + (Y_{i1}^1 - Y_{i0}^0) + a \cdot (Y_{i1}^1 - Y_{i0}^0)
\]
\[= d e f \alpha_i + \tau_i + a \cdot \delta_i.\]
In words, this means that we can decompose the potential outcome score \( Y_{ai} \) of individual \( i \) at endpoint \( t = 1 \) under treatment \( a \) as the sum of the following quantities (Figure 1):

- the baseline score (aka the pre-treatment score) of individual \( i \)
- the temporal change of score (aka the response) of individual \( i \) under control
- the treatment effect of individual \( i \) in case \( a = 1 \) and zero otherwise.

\[ \text{Figure 1: Decomposition of the potential outcomes } Y_{ai}. \]

We then have for the difference in variance in temporal change

\[
\begin{align*}
\text{Var}(Y_{a1} - Y_{a0}) &- \text{Var}(Y_{b1} - Y_{b0}) \\
&= \text{Var}(\delta) + 2\rho \text{Var}(\gamma) \sqrt{\text{Var}(\delta)}
\end{align*}
\]

(1)

Here, \( \rho \) denotes the correlation between \( \tau \), the change (or response) score under control, and \( \delta \), the treatment effect. Note that this quantity is not observable since it contains information about the correlation between both potential outcomes \( Y_{ai} \) and \( Y_{bi} \).

4.1 Compatible values of TEH and VR

With equation (1) at hand, we are ready to derive restrictions on the standard deviation \( \sigma_{\delta} = \text{Var}(\delta)^{\frac{1}{2}} \) of the treatment effect \( \delta \).

Let \( \nu \) be the variability ratio defined with respect to the response variables \( Y^a = Y_{ai} - Y_{a0} \). Then, we have that

\[
\begin{align*}
\nu^2 - 1 &= \frac{\text{Var}(Y_{a1} - Y_{a0}) - \text{Var}(Y_{b1} - Y_{b0})}{\text{Var}(Y_{a1} - Y_{a0})} \\
&= \frac{\text{Var}(\delta) + 2\rho \text{Var}(\gamma) \sqrt{\text{Var}(\delta)}}{\text{Var}(\gamma)} \\
&= \frac{\sigma_{\gamma}^2}{\sigma_{\gamma}^2} + 2\rho \frac{\sigma_{\gamma} \sigma_{\delta}}{\sigma_{\gamma}^2} \\
&= \frac{1}{\sigma_{\gamma}} (\sigma_{\delta} + \rho \sigma_{\gamma})^2 - \rho^2.
\end{align*}
\]

(2)

Now set \( r := \nu^2 - 1 \), then we see that we must have that \( r \geq -\rho^2 \), and we may write

\[
|\sigma_{\delta} + \rho \sigma_{\gamma}| = \sigma_{\gamma} \sqrt{r + \rho^2}.
\]

Hence, we have the following compatible values for \( \sigma_{\delta} \)

\[
\begin{align*}
\sigma_{\delta} &= \sigma_{\gamma} \sqrt{\nu^2 - 1} ; \quad r \geq 0 \\
\sigma_{\delta} &= \sigma_{\gamma} (\pm \sqrt{\nu^2 - 1} - \rho); \quad \rho \leq 0 \text{ and } -\rho^2 \leq r \leq 0.
\end{align*}
\]

Figure 2: Compatible combinations of \( r \) and \( \rho \). Hatched area has two solutions for \( \sigma_{\delta} \).

It is interesting to observe that for negative values of \( r \) (or equivalently, \( \nu < 1 \)) there are two possible solutions for \( \sigma_{\delta} \) as visualized in figures (3) and (4).

Since the quantities \( r = \nu^2 - 1 \) and \( \sigma_{\gamma} \) are estimable from data, the main equation (2) implies the following bound on \( \sigma_{\delta} \):

\[
|1 - \nu| \leq \frac{\sigma_{\delta}}{\sigma_{\gamma}} \leq 1 + \nu.
\]

If we are willing to make assumptions on the values of \( \rho \), e.g. through domain knowledge, this estimate can be improved. In case \( \rho = 0 \) we have that

\[
\sigma_{\delta} = \sigma_{\gamma} \sqrt{\nu^2 - 1}.
\]

From a Bayesian perspective, we may put a distribution on the values of \( \rho \) representing our belief about the true value of \( \rho \), which in turn yields a probability distribution on the values of \( \sigma_{\delta} \).
4.2 Simulations

In this section we conduct a simulation that illustrates the compatibility of a variability ratio of 1 and an average treatment effect of 0 with a TEH of $\sigma_\delta = 1$.

We consider the following toy example. Let $Y^0, Y^1$ be the potential outcome responses under control and treatment, respectively. We let $(Y^0, Y^1 - Y^0)$ have a distribution with mean 0 and covariance matrix $\Sigma$ given by

$$
\Sigma = \begin{pmatrix}
1 & -0.5 \\
-0.5 & 1
\end{pmatrix}.
$$

The following python code generates potential outcomes of this toy model for 10000 units:

```python
import numpy as np
from numpy.random import choice
np.random.seed(1)
rho = -0.5
mu_tau = 0
sigma_tau = 1
mu_delta = 0
sigma_delta = 1
N = 10000
def draw_potential_outcomes(N):
    Sigma = np.array([
        [sigma_tau ** 2, rho * sigma_delta * sigma_tau],
        [rho * sigma_tau * sigma_delta, sigma_delta ** 2]
    ])
    u = np.random.multivariate_normal((mu_tau, mu_delta), Sigma, size=N)
    Y0 = u[:, 0]
    Y1 = Y0 + u[:, 1]
    return Y0, Y1
```

The python code below conducts 1000 simulations of drawing 10000 units from the toy model distribution, calculating the empirical standard deviation of the (unobservable) treatment effect, randomly assigning them into treatment and control groups, and then calculating the VR effect size statistic.

```python
import pandas as pd
simulations = 1000
def get_simulation_df(simulations, N):
```

The python code below conducts 1000 simulations of drawing 10000 units from the toy model distribution, calculating the empirical standard deviation of the (unobservable) treatment effect, randomly assigning them into treatment and control groups, and then calculating the VR effect size statistic.

```python
import pandas as pd
simulations = 1000
def get_simulation_df(simulations, N):
```
df = pd.DataFrame()  
for i in range(simulations):
    Y0, Y1 = draw_potential_outcomes(N)  
    # randomize N units into treatment and control  
    W = np.array([False for _ in range(N)])  
    N1 = int(N / 2)  
    W[choice(range(N), N1, replace=False)] = True  
    Y1_obs = Y1[W]  
    Y0_obs = Y0[~W]  
    SD_treatment = Y1_obs.std(ddof=1)  
    SD_control = Y0_obs.std(ddof=1)  
    VR = SD_treatment / SD_control  
    SD_delta = (Y1 - Y0).std()  
    df = df.append(
        {
            'VR': VR,
            'SD_delta': SD_delta
        }, ignore_index=True
    )
return df

The python code above was used to generate the following visualization of the simulations:

Figure 6: Simulated data of 10000 units with $\nu = 1$ and $\sigma_\delta = 0$.

5 Discussion and Conclusions

The variability ratio (VR) effect size statistic (defined in Hedges and Nowell (1995); and proposed in Nakagawa et al. (2015)) has been used extensively in order to study treatment effect heterogeneity (TEH) in clinical studies. While a VR that is different from 1 is widely acknowledged to implicate a treatment effect heterogeneity (TEH) the exact relationship between those two quantities has not been discussed in detail thus far.

In this note we derived an analytic expression that connects the VR and the standard deviation of the treatment effect that includes an unobservable correlation coefficient. This equation implies precise upper and lower bounds on the the standard deviation of the treatment effect in terms of the VR and the standard deviation of the response under placebo.

In particular, we showed that in case that the variability is equal to 1, the standard deviation of the treatment effect is at most twice the size of the standard deviation of the response under placebo. Moreover, if one is willing to make assumptions on the non-negativity of an unobserved quantity this implies a constant treatment effect. We illustrated our finding with visualizations and a simulation.

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References

Abadie, Alberto, Susan Athey, Guido W Imbens, and Jeffrey M Wooldridge. 2020. “Sampling-Based Versus Design-Based Uncertainty in Regression Analysis.” *Econometrica* 88 (1): 265–96.

Brugger, Stefan P, Ilina Angelescu, Anissa Abidargham, Romina Mizrahi, Vahid Shahrrezaei, and Oliver D Howes. 2020. “Heterogeneity of Striatal Dopamine Function in Schizophrenia: Meta-Analysis of Variance.” *Biological Psychiatry* 87 (3): 215–24.

Brugger, Stefan P, and Oliver D Howes. 2017. “Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-Analysis.” *JAMA Psychiatry* 74 (11): 1104–11.

Hedges, Larry V, and Amy Nowell. 1995. “Sex Differences in Mental Test Scores, Variability, and Numbers of High-Scoring Individuals.” *Science* 269 (5220): 41–45.

Holland, Paul W. 1986. “Statistics and Causal Inference.” *Journal of the American Statistical Association* 81 (396): 945–60.

Maslej, Marta M, Toshiaki A Furukawa, Andrea Cipriani, Paul W Andrews, and Benoit H Mulsant. 2020. “Individual Differences in Response to Antidepressants: A Meta-Analysis of Placebo-Controlled Randomized Clinical Trials.” *JAMA Psychiatry*.

McCUTCHEON, Robert A, Toby Pillinger, Yuya Mizuno, Adam Montgomery, Haridha Pandian, Luke Vano, Tiago Reis Marques, and Oliver D Howes. 2019. “The Efficacy and Heterogeneity of Antipsychotic Response in Schizophrenia: A Meta-Analysis.” *Molecular Psychiatry*, 1–11.

Mizuno, Yuya, Robert A McCutcheon, Stefan P Brugger, and Oliver D Howes. 2020. “Heterogeneity and Efficacy of Antipsychotic Treatment for Schizophrenia with or Without Treatment Resistance: A Meta-Analysis.” *Neuropsychopharmacology* 45 (4): 622–31.

Morgan, Stephen L, and Christopher Winship. 2015. *Counterfactuals and Causal Inference*. Cambridge University Press.

Nakagawa, Shinichi, Robert Poulin, Kerrie Mengersen, Klaus Reinhold, Leif Engqvist, Malgorzata Lagisz, and Alistair M Senior. 2015. “Meta-Analysis of Variation: Ecological and Evolutionary Applications and Beyond.” *Methods in Ecology and Evolution* 6 (2): 143–52.

Plöderl, Martin, and Michael Pascal Hengartner. 2019. “What Are the Chances for Personalised Treatment with Antidepressants? Detection of Patient-by-Treatment Interaction with a Variance Ratio Meta-Analysis.” *BMJ Open* 9 (12).

Raudenbush, Stephen W, and Anthony S Bryk. 1987. “Examining Correlates of Diversity.” *Journal of Educational Statistics* 12 (3): 241–69.

Rogdaki, Maria, Maria Gudbrandsen, Robert A McCutcheon, Charlotte E Blackmore, Stefan Brugger, Christine Ecker, Michael C Craig, Eileen Daly, Declan GM Murphy, and Oliver Howes. 2020. “Magnitude and Heterogeneity of Brain Structural Abnormalities in 22q11.2 Deletion Syndrome: A Meta-Analysis.” *Molecular Psychiatry*, 1–14.

Senior, Alistair M, Alison K Gosby, Jing Lu, Stephen J Simpson, and David Raubenheimer. 2016. “Meta-Analysis of Variance: An Illustration Comparing the Effects of Two Dietary Interventions on Variability in Weight.” *Evolution, Medicine, and Public Health* 2016 (1): 244–55.

Spiegelhalter, David. 2019. *The Art of Statistics: Learning from Data*. Penguin UK.

Volkmann, Constantin Michael Dimitri, Alexander Volkmann, and Christian Mueller. 2020. “On the Treatment Effect Heterogeneity of Antidepressants in Major Depression. A Bayesian Meta-Analysis.” medRxiv.

Winkelbeiner, Stephanie, Stefan Leucht, John M Kane, and Philipp Homan. 2019. “Evaluation of Differences in Individual Treatment Response in Schizophrenia Spectrum Disorders: A Meta-Analysis.” *JAMA Psychiatry* 76 (10): 1063–73.