Association Between BCG Policy is Significantly Confounded by Age and is Unlikely to Alter Infection or Mortality Rates

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Abstract

Recently a number of publications looked at the association between COVID-19 morbidity and mortality on one hand and the countries' policies with respect to BCG vaccination on the other. This connection arises from differences in the rates of infection in countries where BCG vaccination is mandatory compared to countries where mandatory vaccination no longer exists or was never implemented in the first place. In at least 2 preprint publications the authors expressed the view that the "known immunological benefits" of BCG vaccination may be behind the biological mechanism of such observation.
One study accounted for different income levels in different groups. Another study did not attempted to do so, instead exploring the differences between countries where a booster shot is given vs others where no such practice exists and finding no connection.
Both of these studies did not explore other potential confounding factors. At the same time the general press has seized the headline and pushed the narrative that BCG vaccination is causally linked to infection and mortality rates. This presents a serious challenge, demonstrated by the recently initiated clinical trials on BCG vaccination within the COVID19 context.
This study shows that population age is a very significant confounding factor that explains much better the rates of infections and has solid biology mechanism explaining this correlation. This study suggests that BCG vaccination may have little or no causal link to infection rates and advises that any follow up studies should control for several confounding factors, such as population age, ethnicity, rates of certain chronic diseases, time from community spread start date, major public policy decisions and income levels.

Introduction

BCG vaccine has been associated in multiple studies with effects beyond protection against tuberculosis, which is the original target of the intervention(1). As such, BCG vaccine has been shown to enhance the protection provided by H1N1 vaccine(2). Another study observed that preceding BCG vaccination attenuates yellow fever vaccine associated viremia(3). These findings prompted two independent studies(4,5) in which a strong correlation between the presence of BCG vaccination and rate of COVID19 infections and/or death rates was observed.

These observations were also communicated by the press in general (6–9). While some of these publications contacted additional subject matter experts who cautioned that the studies are not yet perr reviewed and urged patience(7), there is danger that the observations will be over interpreted and used for policy decisions. For example, there are currently at least 2 ongoing studies focusing on the effect of BCG vaccination in the context of COVID19 infections(10).
Given the extreme urgency and the potential for serious consequences we decided to explore this matter in more depth.

Materials and Methods

Data on average population age per country and number of infections was collected from Wikipedia. BCG policy and income level data was obtained from one of the original studies. BCG and rubella immunization rates were obtained from WHO website(11).
Country names were cleaned and data was merged in R (Rstudio 1.1.456 on Ubuntu 16 Linux, R version 3.2.3). All scripts and data files are available from https://github.com/kirovsa/covid19-bcg.
As with one of the original studies we excluded countries with population of less than 1M. For analysis of death rates we also excluded countries with no deaths recorded as these are likely to be in the very initial phase of the epidemic and likely to introduce significant noise.
To determine the effect of different factors we used lm function from stats package. Evaluating factors effects on infections in the presence of random effect was done with lme from nlme package. Log likelihood was tested with lrtest from lmtest package.

Results

Based on significant amount of accumulated data we are aware that age is the most significant factor predicting hospitalization of COVID19 patients and fatal outcomes. Younger people also seem to be more likely to remain asymptomatic. Therefore we decided to evaluate a linear regression model that accounts for 3 factors- BCG policy, income level and median age per country.
While the model as a whole explains very well the differences in infection rates across countries, the most significant factor was income level, followed by median age. BCG policy was significant but lagged the other factors (Figure 1). However, BCG immunization rates was not significant in this model at alpha level at 0.05 ($p=0.088$). The likelihood test did find that the BCG policy had an effect ($p=0.0028$) compared to the full model, however this was not true for BCG vaccination rates ($p=0.08$). If there is a causal link between BCG vaccination and COVID19 infection rates we would expect this association to hold or even get stronger, something we did not find evidence for.
The Pearson correlation between median age and infection rates was also much higher at $R=0.774$ than the reported correlation between the BCG policy and the infection rates at $R=0.521$ or the reported correlation between start date of BCG vaccination and infection rates ($R=0.21$).
The correlation between number of cases per million people with the median age in a country does not change substantially between different policy categories (Figure 2A), though there was some separation between categories 1 and 3. We can evaluate this however only for countries with high rates of infection and also higher median age. When the BCG immunization rates were used instead of the policy we saw no association (Figure 2B).
We also explored potential connection between countries with higher rubella immunization rates vs those with lower rates (separated in categories by 50% threshold) and COVID19 infections. While this variable by itself showed significant association ($p<0.0001$) with the observed rates per country, it appeared that the effect is the opposite of what would be expected (Figure 2C) with countries with low

immunization rates scoring better in terms of infection rate and disappeared after we included other factors such as median age and income level ($p=0.056$).
Since income levels are unlikely to drive infection rates we decided to compare the performance of median age and BCG policy. We found that median age explains the variance in the number of COVID19 cases better than the BCG policy either with or without income level adjustment (Figure 3). The median age explained 60% of the variability vs 30% for BCG policy. Finally, we used income levels as a random factor in a mixed model. In this context median age again appears to be more important than BCG policy (Figure 4). BCG rates were again non-significant at $p=0.0798$.
Next, we looked at the median age distribution in different income levels and BCG policy categories (Figure 5). There is strong association between median age and BCG policy with or without income level adjustment ($p<0.0001$). The same is true for median age and income level ($p<0.0001$).
Next we looked at the deaths per million (Figure 6). Again, we saw better correlation between median age and death rates ($R=0.653$) compared to the correlation between start date of BCG vaccination policy reported in one of the studies ($R=0.54$).
BMI was another strong confounding factor in the context of mortality rates(Figure 7). Countries with normal BMI were without exception in the policy category 1 (mandatory BCG vaccination). In addition, death rates were substantially higher in countries with high BMI ($p<0.0001$).

Discussion

While observational studies are a valid and useful tool, there are also serious obstacles interpreting the data correctly(12). In the specific case of the correlation between BCG vaccination policy and COVID19 outcomes it is clear that important confounding factors may have been missed. An excellent outline of these was given by Emily MacLean(13). In addition to missing hidden factors, the critique in the blog goes further to challenge the biological plausibility of the BCG vaccine-COVID19 connection. It seems this is a very reasonable concern, given that the only established connection between BCG vaccination and protection against viral infections seems to be within the scope of actual anti-viral vaccines(2,3) or booster effect. On the other hand, the biological rational for causal link between age and COVID19 morbidity and mortality seems a lot more straightforward; if we follow the Occam's razor we should prioritize this link over BCG vaccination. We also want to emphasize that the association we observed between infection rates and rubella immunization are almost certainly spurious. The arguments we see so far is that early childhood vaccinations might be protective, which is the opposite of our observation. We also want to highlight preclinical research(14) that was done during one of the previous coronavirus crisis- and it shows clearly that childhood vaccinations are unlikely to drive different outcomes of COVID19 infections.
This is further enhanced by the data we presented in this study. We also need to emphasize that we have not included a number of other potentially confounding factors such as blood pressure, public policy (mandatory travel restrictions, use of masks, etc.) or time from first infection. Finally, any conclusive study will need to address the disagreement between BCG policy and actual BCG vaccination rates with the first still contributing to the regression model, whereas the second did not.

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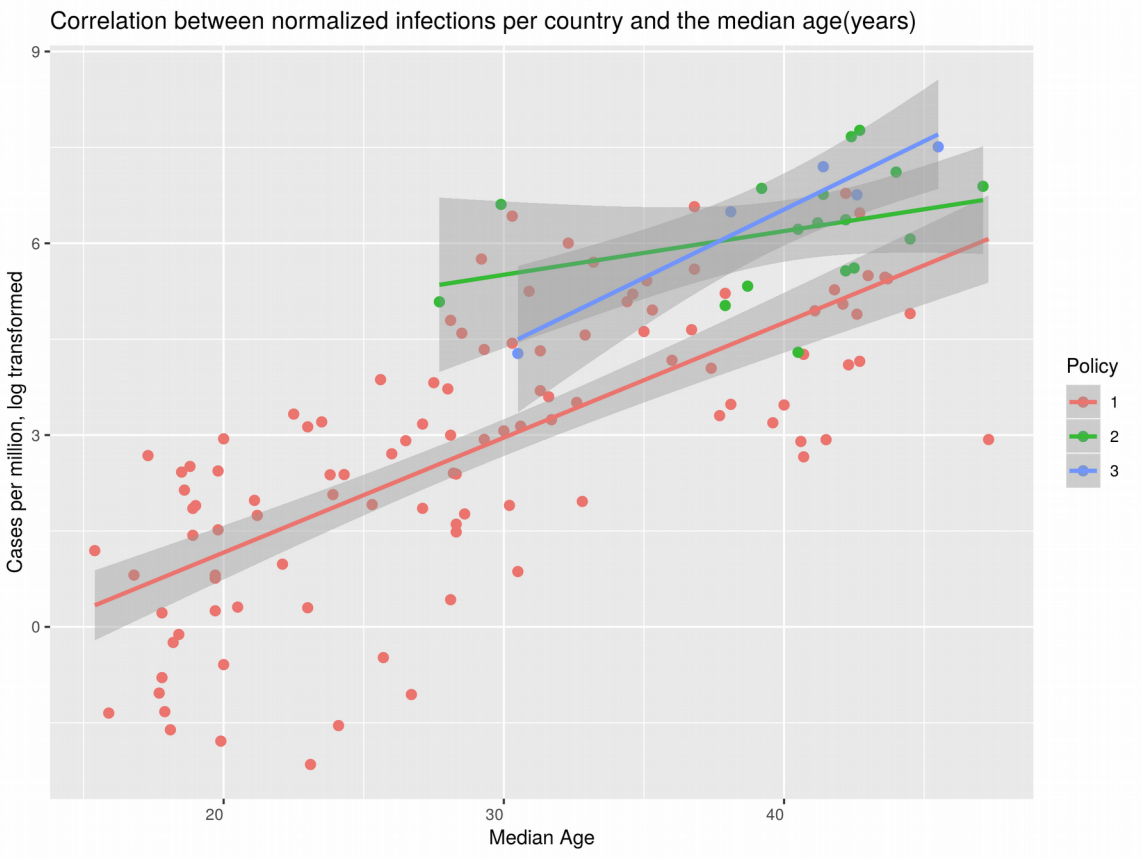
Figures and tables

Figure 1. Linear regression model exploring policy, age and income level effect on infection rates

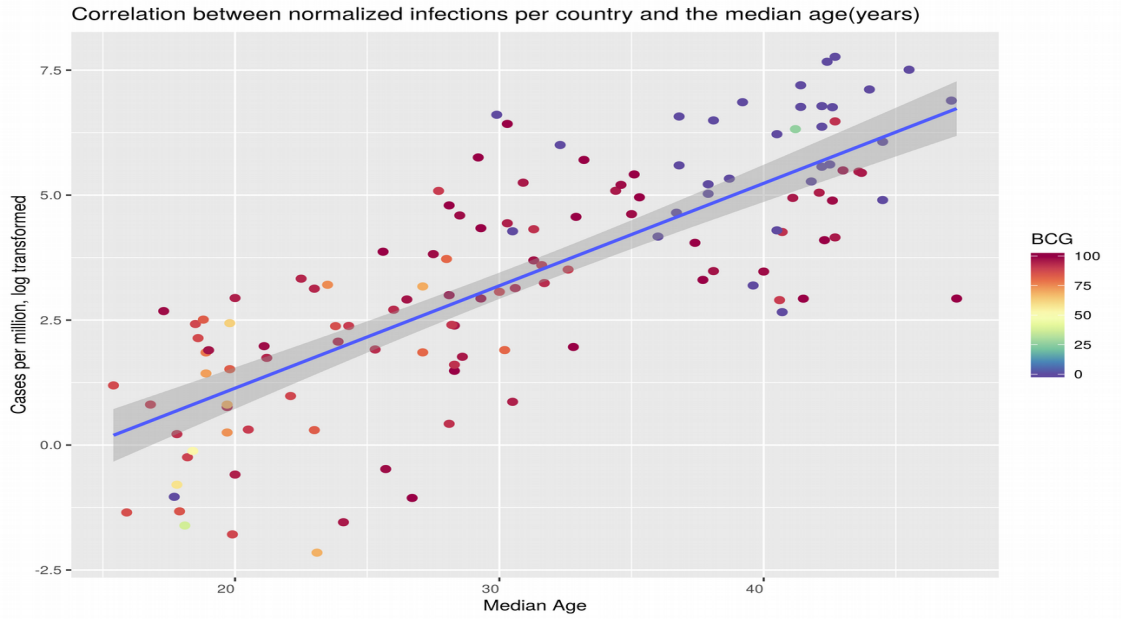
```
Call:
lm(formula = log(CasesPerM) ~ Median + Policy + IncomeLevel,
    data = covid.stage2)

Residuals:
    Min      1Q  Median      3Q     Max
-3.3978 -0.7759 -0.0137  0.9219  2.9194

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  -1.16279    0.48224  -2.411  0.01738 *
Median        0.07980    0.01968   4.054 8.86e-05 ***
Policy2       1.06411    0.38036   2.798  0.00598 **
Policy3       1.48048    0.58576   2.527  0.01276 *
IncomeLevel2  0.56466    0.39583   1.427  0.15625
IncomeLevel3  2.25019    0.43483   5.175 8.99e-07 ***
IncomeLevel4  3.14738    0.54213   5.806 5.12e-08 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1.222 on 123 degrees of freedom
Multiple R-squared:  0.7463,  Adjusted R-squared:  0.734
F-statistic: 60.32 on 6 and 123 DF,  p-value: < 2.2e-16

Call:
lm(formula = log(CasesPerM) ~ Median + BCG + IncomeLevel, data = covid.stage2)

Residuals:
    Min      1Q  Median      3Q     Max
-3.4935 -0.7091  0.0879  0.9235  2.9354

Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)  -0.788849   0.594703  -1.326   0.1871
Median        0.083537   0.020396   4.096 7.54e-05 ***
BCG          -0.005930   0.003453  -1.717   0.0884 .
IncomeLevel2  0.609350   0.411892   1.479   0.1416
IncomeLevel3  2.334206   0.455878   5.120 1.13e-06 ***
IncomeLevel4  3.365031   0.551903   6.097 1.26e-08 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1.258 on 124 degrees of freedom
Multiple R-squared:  0.7288,  Adjusted R-squared:  0.7179
F-statistic: 66.64 on 5 and 124 DF,  p-value: < 2.2e-16
```

Figure 2. Relationship between median age per country and infection rates in the context of BCG policy

A



B



C

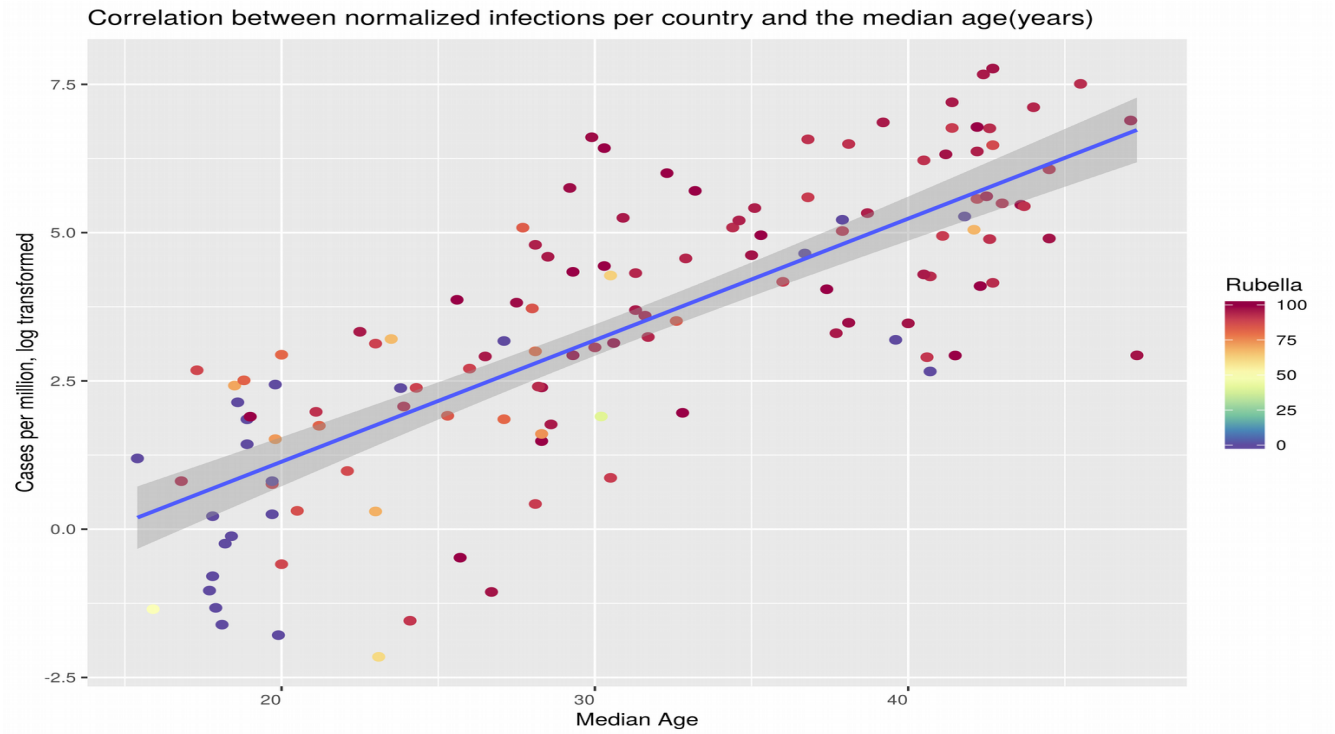

Correlation between normalized infections per country and the median age(years)
Cases per million, log transformed
7.5
5.0
2.5
0.0
-2.5
20
30
40
Median Age
Rubella
100
75
50
25
0

Figure 3. Effect of BCG policy or median age and infection rates in the presence and absence of income level effect

```
> anova(lm(log(CasesPerM) ~  Policy + IncomeLevel, data= covid.stage2))
Analysis of Variance Table

Response: log(CasesPerM)
             Df Sum Sq Mean Sq F value    Pr(>F)
Policy        2 219.53 109.763  65.376 < 2.2e-16 ***
IncomeLevel   3 296.29  98.763  58.825 < 2.2e-16 ***
Residuals   124 208.19   1.679
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
> anova(lm(log(CasesPerM) ~  Median + IncomeLevel, data= covid.stage2))
Analysis of Variance Table

Response: log(CasesPerM)
             Df Sum Sq Mean Sq F value    Pr(>F)
Median        1 433.67  433.67 269.662 < 2.2e-16 ***
IncomeLevel   3  89.31   29.77  18.511 5.329e-10 ***
Residuals   125 201.03    1.61
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
> anova(lm(log(CasesPerM) ~  Policy , data= covid.stage2))
Analysis of Variance Table

Response: log(CasesPerM)
           Df Sum Sq Mean Sq F value    Pr(>F)
Policy      2 219.53 109.763  27.632 1.089e-10 ***
Residuals 127 504.48   3.972
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
> anova(lm(log(CasesPerM) ~  Median, data= covid.stage2))
Analysis of Variance Table

Response: log(CasesPerM)
           Df Sum Sq Mean Sq F value    Pr(>F)
Median      1 433.67  433.67  191.19 < 2.2e-16 ***
Residuals 128 290.33    2.27
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Figure 4.

Fixed effects: log(CasesPerM) ~ Median + Policy

	Value	Std.Error	DF	t-value	p-value
(Intercept)	0.1470049	0.8923356	123	0.164742	0.8694
Median	0.0864087	0.0193181	123	4.472947	0.0000
Policy2	1.0936249	0.3796067	123	2.880942	0.0047
Policy3	1.5033315	0.5856559	123	2.566920	0.0115

Fixed effects: log(CasesPerM) ~ Median + BCG

	Value	Std.Error	DF	t-value	p-value
(Intercept)	0.6196404	1.0028649	124	0.617870	0.5378
Median	0.0902190	0.0200332	124	4.503473	0.0000
BCG	-0.0060820	0.0034438	124	-1.766091	0.0798

Figure 5. Relationship between median age and BCG policy in the context of income levels

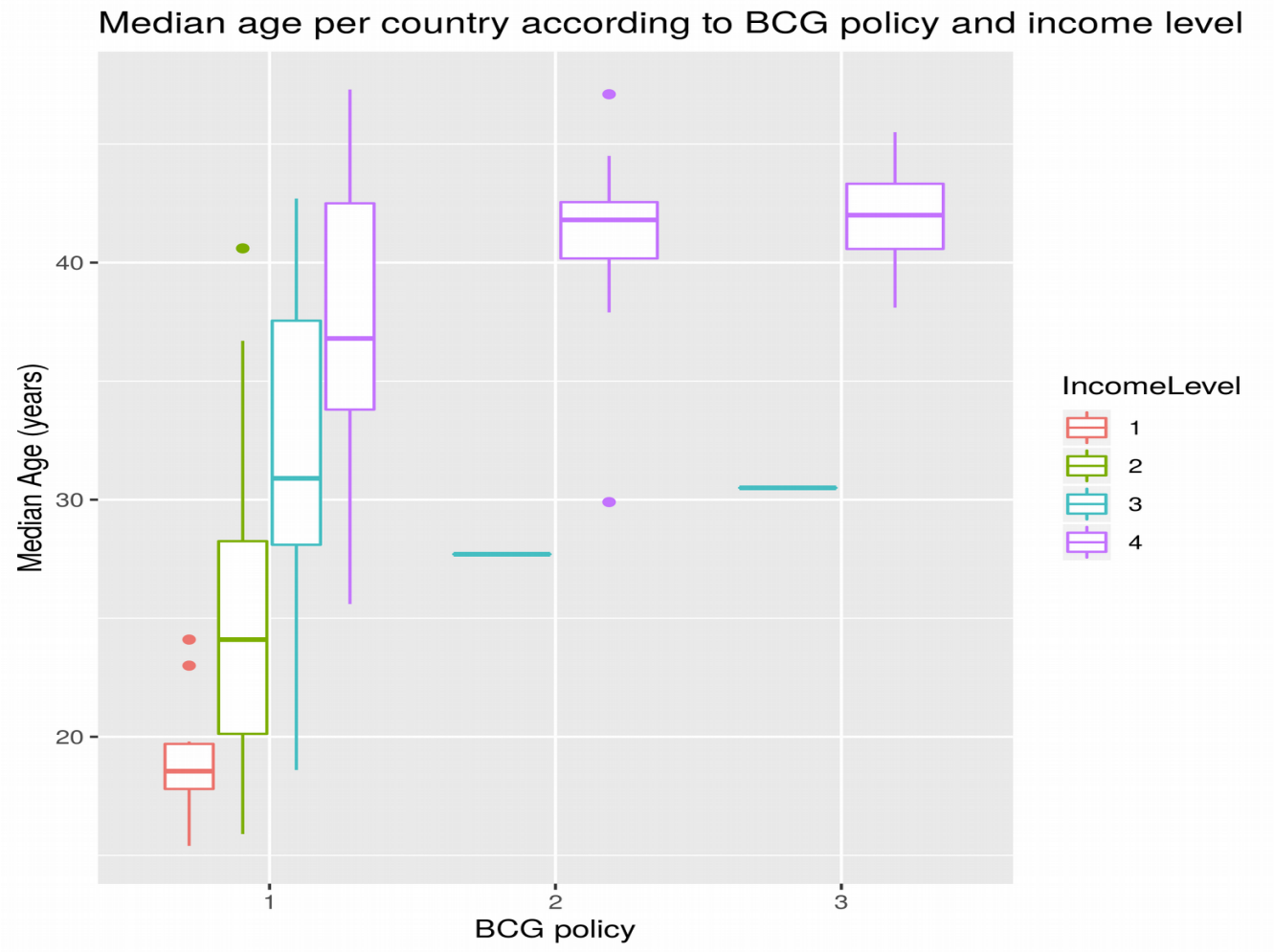


Figure 6.

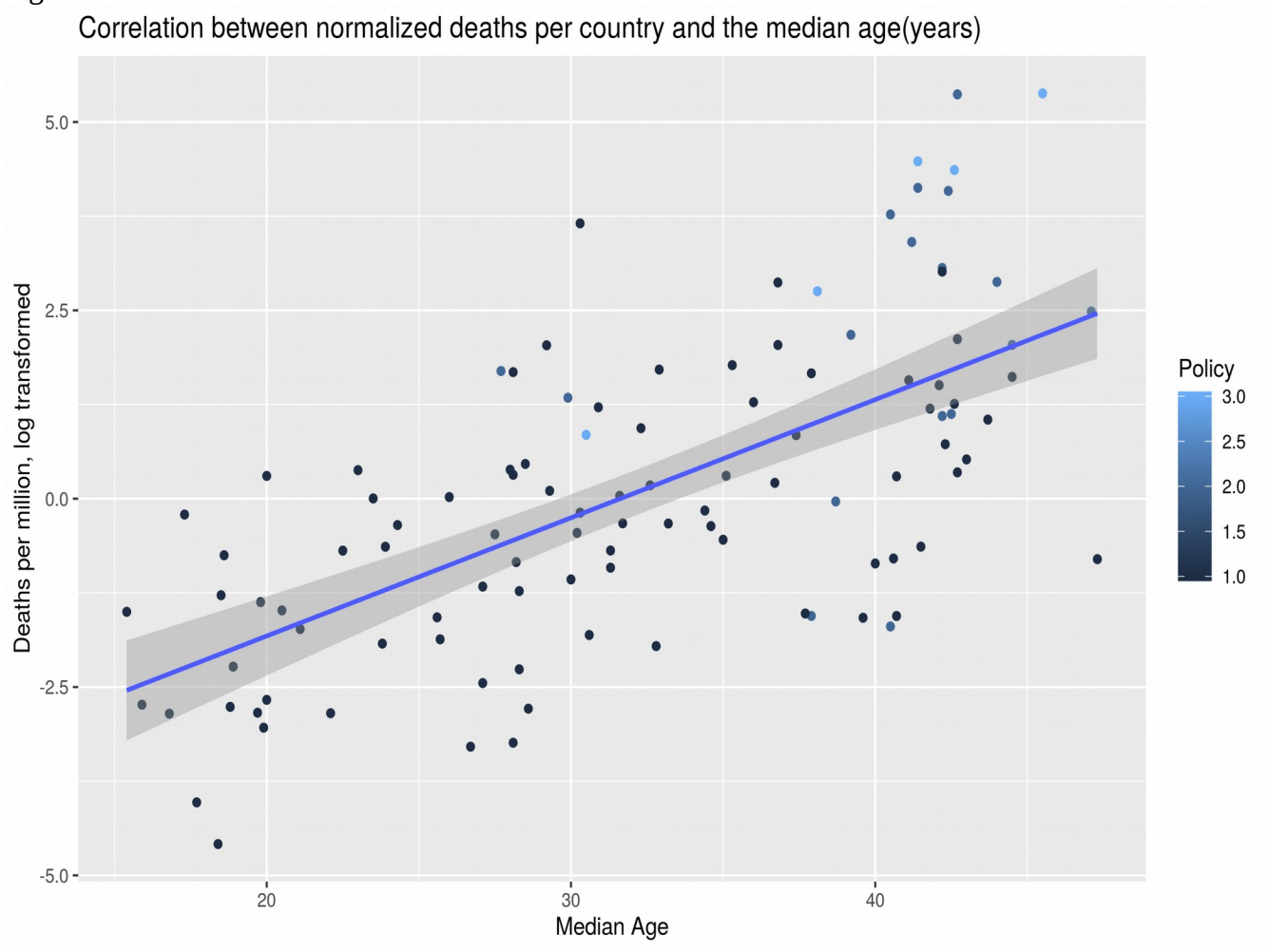
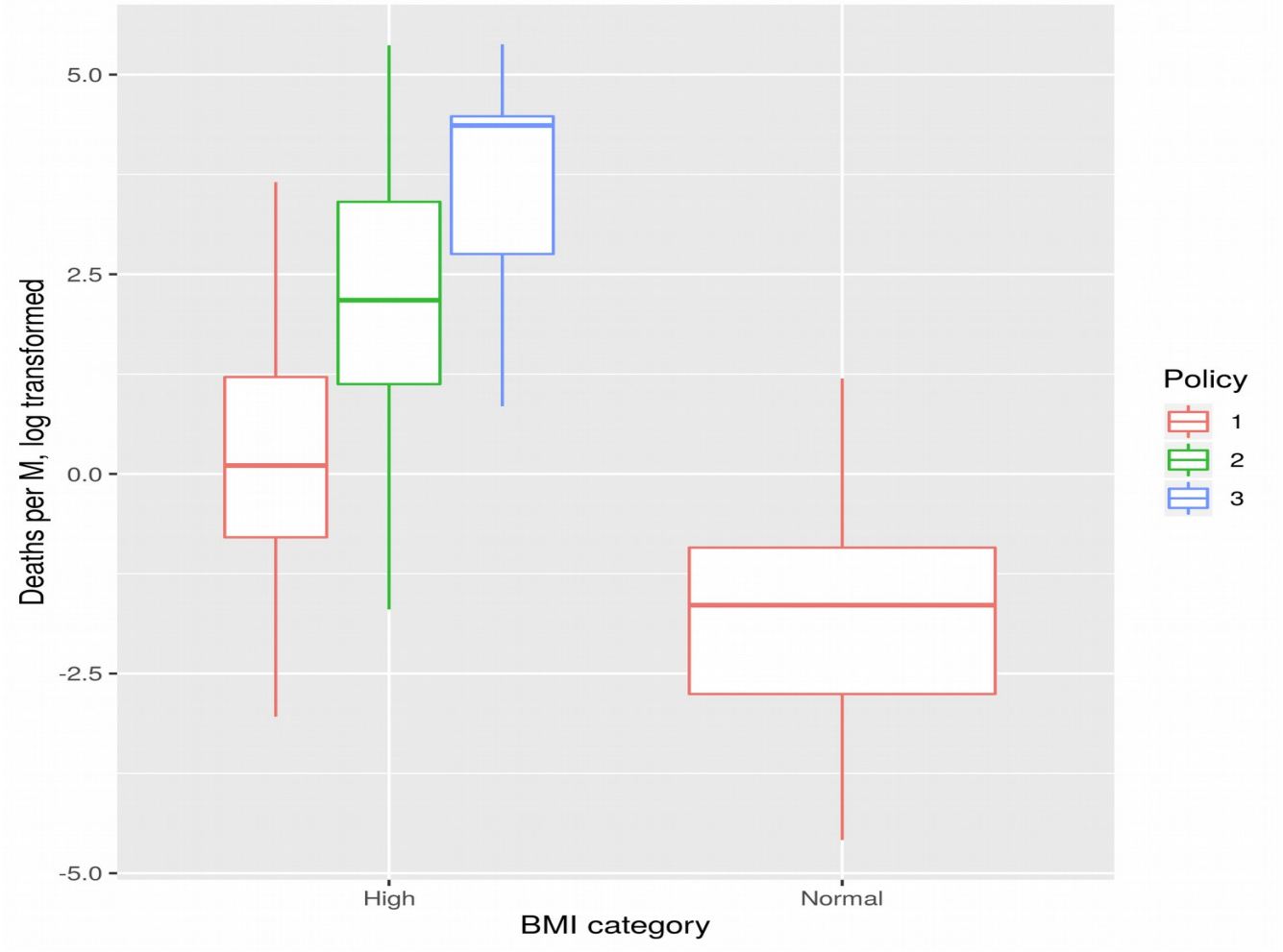

Correlation between normalized deaths per country and the median age(years)
Deaths per million, log transformed
5.0
2.5
0.0
-2.5
-5.0
20
30
40
Median Age
Policy
3.0
2.5
2.0
1.5
1.0

Figure 7. Association between normalized deaths from COVID19 and BMI (high>25) in the context of BCG policy



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