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#### Kirsten Bibbins-Domingo, PhD, MD, MAS

###### Editor in Chief, Journal of The American Medical Association (JAMA)

Lee Goldman, MD Endowed Professor of Medicine and Professor of Epidemiology and Biostatistics

University of California San Francisco,

San Francisco, California, U.S.A.

Dear Dr. Bibbins-Domingo,

Please find the manuscript, titled “*Association of Posttraumatic Growth with Covid-19 and Posttraumatic Stress: A Meta-analytic Review,*” uploaded to the Journal of The American Medical Association (JAMA) submission site. We hope that itbe considered for review by your editorial board. The manuscript has not been previously published nor is it under consideration at another outlet; furthermore, the findings have not been posted online.

We assume that the finding will be of interest to the readers of *JAHA* because this interdisciplinary study provides information on an aggregated outcome, PTG, in populations exposed to the Covid-19 Pandemic, the deadliest global disaster in the 21 century. The under-investigated positive side of the major threat to humanity may have implications for patient-centered preventive and clinical care in coming decades.

All authors have contributed substantively to developing this manuscript and agreed to be a co-author. The authors declare that there are no conflicts of interest. Because this first meta-analysis on this topic in the context of Covid-19 use only published data, the human subject application is not relevant. We do not know which sub-journal under the system of *JAMA* will be suitable for this topic. But we trust that you will direct it to the appropriate one.

To make the manuscript short, all subgroup figures are in the Appendix for provision upon request. If you consider that they are acceptable within the desirable length, we can put it back.

Finally, congrats for you to be the first woman of color to serve on this honorable position! Thank you for your attention! We look forward to hearing your editorial decision.

Amy L. Ai, PhD

FSU Distinguished Research Professor

**Association of Posttraumatic Growth with Covid-19 and Posttraumatic Stress:**

**A Meta-analytic Review**

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**(Running Head: Covid-19 and PTG)**

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**Association of Posttraumatic Growth with Covid-19 and Posttraumatic Stress:**

**A Meta-analytic Review**

**Abstract: Importance** Posttraumatic growth (PTG) can be easily assessed and potentially lead to optimal outcomes of the patients, health providers, and general populations affected by Covid-19. **Objective**To conduct the first meta-analysis and systematic review of the association between PTG and Covid-19 and posttraumatic stress symptoms (PTSS). **DATA SOURCES AND STUDY SELECTION** PubMed, PsychINFO, Academic Search Complete (?), Ovid MEDLINE (?), … and… (Marg) electronic databases were systematically searched from …… through August 20, 2023, (Marg, pls to do one more search) to identify all eligible studies reporting the association between PTG and Covid-19 by suing the following Medical Subject Heading and psychological terms: Covid-19, PTG, ….. (Marg). **DATA EXTRACTION AND SYNTHESIS** Data were screened and extracted independently by 2 investigators(A.A. and Q.D.). Adjusted effect estimates were employed, and pooled analysis was conducted, using the Hartung-Knapp-Sidik-Jonkman rondom-effects model. Sensitivity and subgroup analyses were conducted to assess the robustness of the findings. The Meta-analysis of Observational Studies in Epidemiology(MOOSE) reporting guideline was followed (QZ). **MAINOUTCOMES AND MEASURES** …. (QZ). PTSS was assessed as a separate outcome with PTG. **RESULTS** The search yielded 24 selected studies comprising 4….. participants of which …?? studies presented data on the COVID-19-PTG association, and …?? presented data on PTSS. On pooled analysis, COVID-19 was significantly associated with PTG (Weighted mean …-…..; 95% Cim 0….-0….; *P* < .001), with a moderate heterogeneity in the analysis(*I*2 = …..%). Subgroup analyses indicated the link between Covid-19 related PTG and PTSS in COVID-19 (QZ???). **Conclusion and Relevance** The findings indicate that COVID-19 events could be associated with PTG as a potential positive outcome. Future investigation should pursue more prospective design and explore the biobehavioral mechanisms underlying this relationship to promote PTG-related better outcomes in patient-centered care. (250 words + four subtitles).

**Key Points**

**Question** Is Covid-19 potentially associated with posttraumatic growth among patients, health care providers, and general population globally exposed to the deadly pandemic?

**Findings** In this meta-analysis 24 studies including 4….. individuals, PTG was associated with individuals exposed to Covid-19 in both medical settings and beyond; the pooled association was consistent with that of findings from studies with diverse populations.

**Meaning** The findings suggest that an optimal outcome, posttraumatic growth, could occur among various populations affected by Covid-19 and that attention to this positive side of this global existential threat may be important for mental and public health during the pandemic.

***Keywords:*** Meta-analysis and systematic review, cardiovascular disease (COVID-19), post-traumatic growth (PTG), myocardial infarction, stroke, cardiac procedures

COVID-19 is also the number one killer of all American subgroups with an average annual direct and indirect cost of an estimated $407.3 billion in the United States from 2018 to 2019 (Tsao et al., 2023). Given the significant public health impact, epidemiological and clinical research on COVID-19 has focused primarily on its pathological outcomes and mortality risks, such as depression, anxiety and posttraumatic stress disorder (PTSD) (Bozkurt, 2021; Davidson et al, 2018; Dornelas & Sears, 2018; Edmondson et al., 2013; Stoney et al, 2018; Wu & Kling, 2016).

In an era of patient-centered care, however, treatment for COVID-19 patients does not end up with in-hospital and medical intervention, nor life-or-death solutions (Marques et al., 2021). More research is needed for examining the potential positive changes after experiencing severe COVID-19 conditions to boost patients’ quality of life (QOL). One of such outcomes is posttraumatic growth (PTG), defined as the “experience of significant positive change arising from the struggle with a major life crisis” (Calhoun & Tedeschi, 2006). Life-threatening trauma (e.g., COVID-19 events) may shatter existing schemas and give rise to a subsequent alteration of perspectives or priorities in life (Linley & Joseph, 2004). PTG may pertain to the reconstruction of one’s worldviews in several enhanced dimensions: a) *sense of self identity and strength*, b) *appreciation of life*, c) *new priorities*, d) *meaningful relationships* and, and e) *existential life and spirituality* (Tedeschi & Calhoun, 1996). Despite being seemingly paradoxical, PTG reflects a new sense of the world, or a reconstructed worldview, rising from trauma and life-altering events. In other words, it is a desirable adaptation to adversity (Ai et al., 2011; Janoff-Bulman, 2004; Joseph & Linley, 2005).

Growing medical and cardiac research has examined the PTG phenomena in COVID-19 patients (Ai et al., 2011…..

Most studies on PTG in COVID-19 have explored factors related to this positive change. With respect to coping strategies, …..

A systematic meta-analytic review could provide more reliable and less biased conclusions to advance the area of research that bridges trauma psychology to behavioral COVID-19 care. This meta-analytic review, thus, employed a systematic approach to synthesize empirical studies examining PTG in COVID-19. We aimed to reach a more creditable conclusion for an urgent question: Whether personal growth could be observed among patients with COVID-19 despite its detrimental impact on individual and public health..

Based on the literature, we also ….. We expected that depression or PTSD (QZ?) would be inversely related to PTG.

# **Methods**

# **Data Sources and Searches**

This systematic meta-analytic review was conducted and presented according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (Stroup et al., 2000 QZ! -- not sure what I should do here; should I download the paper and read it?). A systematic literature search of Ovid MEDLINE, PsycINFO, Academic Search Complete, and PubMed was performed for research articles published from 2000 since the first year of Covid-19, to 2023 (MC!) but especially 1995, when PTG was coined (Tedeschi & Calhoun, 1995). The following Medical and Psychological Subject Heading terms were used to identify studies that assessed PTG in patients with COVID-19: posttraumatic growth, stress-related growth, adverse growth, COVID-19 MI, ….. (MC!). Furthermore, references from selected studies and relevant review articles were reviewed to identify additional publications.

# **Study Selection**

Two investigators (A.A., Q.D) independently reviewed the potential candidates for this review. Eligible studies were original empirical research articles that assessed posttraumatic and adulthood growth related terms in different types of people who had various with the global pandemic (e.g., patients, health providers, community dwellers, etc.). Studies on other pandemic only (e.g., Ebola, influenzas) or other disasters were excluded. Then, any studies that did not employ an established and validated scale that specifically focused on personal growth (e.g., PTG Inventory/PTGI; Tedeshi & Calhoun, 1996; stress-related growth scales/SRGS, Cohen, & Murch, 1996, Park & Blumberg, 2002) were not included. Excluded studies might use other types of measures on broad positive changes (e.g., Benefit Finding Scale by Mohr et al. 1999; Perceived Benefit Scale by McMillen & Fisher, 1998), because certain gains did not pertain to adulthood growth. Open-ended measures of growth were also excluded due to the lack of validation. In the final selection, only studies with reported mean scores on PTGI, PTGI-SF, or forms that measures similar constructs with standard deviation were included .

**Data Extraction and Quality Assessment**

According to preplanned protocol and using a standardized form, an assistant investigator (M.C.) reviewed all abstracts first to identify potential studies for inclusion. Full text articles were obtained for all potentially eligible studies and were independently reviewed by other two investigators (A.A., Q.D.). Disagreement on the selected studies were then discussed for finalizing the sample. Next, the second reviewer (Q.D.) extracted data from the selected studies. The following data were extracted: study characteristics (e.g., author, year of publication, sample size, study design), patient characteristics (e.g., age, gender, COVID-19 diagnosis), PTG assessment tools, and estimates of the association between PTG and COVID-19 (e.g., t-value or correlation coefficients MC! QZ!). The quality of the selected studies was assessed using the Cochrane Risk of Bias tool (Higgins JPT, et al., 2016 QZ!).

**Statistical Analysis**

R(version 4.3.0) was used to conduct the meta-analysis. The study employed DerSimonian and Laird random-effects model (DerSimonian 1986) to estimate the correlation between PTG and COVID-19. Only study employed a selection criterion for articles reporting the mean and standard deviation (SD) of Posttraumatic Growth (PTG) as assessed by the Posttraumatic Growth Inventory (PTGI) developed by Tedeschi and Calhoun (1996). The Posttraumatic Growth (PTG) measure used in this study involved summing up ratings across 21 self-reported questions, resulting in a possible score range of 0 to 105. The weighted mean of PTGI was used to identify the level of PTG on COVID-19 patients. To categorize the level of PTG, a cutoff point was established: scores of 45 or below indicated none to low levels of PTG, while scores of 46 or above indicated medium to high levels of PTG (based on the literature 45 is a reasonable cutoff point and thus will be used in the main analysis)This method of categorizing the level of PTG based on a predetermined cutoff point allows for a clear distinction between individuals with varying levels of PTG and facilitates the interpretation of study findings. Both models will use I2 to assess the heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). Under 50% of I2 would be considered as a low level of heterogeneity and a fixed effect model would be applied instead of the random effect model. And a forest plots were generated to summarize the results of multiple studies and compare the effect size of exposure across different studies. (QZ!). (A high I^2 indicates high level of heterogeineity, we will use random intercept model, and from then on we can consult tau^2 for accurate representation of the between study heterogeineity.)

Random effects meta-analyses were used to estimate the correlation between various variables and Posttraumatic Growth (PTG) levels. In cases where data were available from at least three studies, these analyses were conducted. Final estimated effect size with 95% CI would be reported to assess the association between PTG and different variables. I2 was also used to assess the heterogeneity and 50% above indicated medium to high levels of heterogeneity QZ!). The I^2 for the PTGI stduies is 99.05%, and for PTGI-SF is 99.92%.

**Results**

**Study Characteristics**

Identified articles were in English, though no language restriction was used to cover publications in both the United States and abroad. Figure 1 illustrates a flow diagram of the literature and related screening process. The search yielded 35 unique publications, of which 24 ( QZ!--yes) qualified for full-text review. In the end,19(Now we only incude PTGI or PTGI-SF, which leaves us with 19 studies) studies (citations of them….. MC! -- in AMA format at the reference section?) met the inclusion criteria for the main analysis. #? (QZ!) studies were selected for subgroup analyses on PTSD citations of them (….. QZ! MC! -- ) . Of these 19 included in the analysis, all employed PTGI or PTGI-SF to examine PTG in not just cardiovascular patients right? Eleven were cross-sectional studies and seven were prospective studies (we need another column in t1 raw for this – this can be useful for subgroup analysis). For the selected studies involving a total of  36743 individuals, table 1 and table 3 present their overall characteristics.

Among the studies included in the analysis, #? studies were performed in the United States (citations….MC?), #? in the United Kingdom (…..), #? in Poland (…..), #? in China (….), two …. (….MC?), in the Netherlands (Garnefski et al., 2008), in Pakistan (Javed & Dawood, 2016), in Israel (….MC?), in Germany (….MC?). Included articles involved a variety types of people (patients, nurses, ……MC?); most of which centered on a single condition or event. → 5 from US, 4 from China, 1 from Iserael, 1 from Ghana, 1 from Greece, 1 from Hongkong, 1 from Norway, 1 from Pakistan, 1 from Saudi, 1 from spain, 1 from turkey, and 1 from Wales. (the code for this can be found in the ptg main analysis script on github)

- this paragraph may be inapplicable.

**Main analysis**

The main included a total of 19 studies, involving a total of 36k…. individuals. The sample size of these studies ranged from #? 176) to 12686? (…….MC?). Most of the studies had a significant proportion of male participants, with the percentage ranging from ??% (….) to ??% (…..). Mean age of them ranged from ??.? (….MC?) to ??.? (….MC?) years. The mean age of the participants varied with studies, with a few not providing explicit data, but indicating that the participants were adults above 18 years old (….). The mean PTG ranged from ??.? (….) to ??.? (….QZ?), with varying degrees of standard deviation, indicative of the range and spread of PTG scores in these studies. Table 1 presents overall characteristics of all studies. → need to standardize the numbers in the t1 raw column for age and gender.

The meta-analysis was conducted using a fixed-effects model instead of the presupposed random-effect model due to low heterogeneity. …. (….QZ?) we use random intercept due to high level of heterogeniety.

For PTGI studies, a significant positive chance in ptg is detected (0.8369, p-value < 0.0001), and for PTGISF, we did not obtain a significant chance in ptg (0.2472, p-value = 0.47), however it is positive change, and subgroup analysis might reveal the story behind it (more sample, more population demographics)

**Subgroup Analyses**

Table 4 shows the summary of subgroup analysis on PTSD???? , ….(….QZ?) look for anxiety, depression, stress instead if PTSD is not applicable?

***Age***

The influence of age on PTG was examined across five studies, involving a total of ?? participants (….). The pooled effect size yielded a value of 0.0? shown in Figure 7, indicating a small positive correlation between age and PTG. The 95% confidence interval, ranging from -0.12 to 0.20, suggests that age could have a slightly favorable impact on the experience of PTG. However, the I2 statistic of ??.??% indicated a significant level of heterogeneity among the selected studies.

***Gender***

The relationship between gender and PTG was analyzed in four studies (this is not final number right?), with a total of ?? participants (….) reveal. The pooled effect size revealed a small positive correlation shown in Figure ?, with a value of 0.??, indicating that gender might played a slightly positive role in the degree of PTG. The 95% confidence interval, ranging from 0.0? to 0.??, suggests a relatively consistent effect across the studies. However, the ?? statistic of ??.??% indicated a low level of heterogeneity among the examined studies, indicating a certain degree of consistency in the relationship.

**Discussion**

….

**Subgroup Analyses of PTG and Covariates**

….

**Mechanisms**

….

**Implications and Conclusions**

This meta-analytical review provides compelling evidence for PTG associated with

Despite the limitations and heterogeneity across studies,

Prospective design with large samples for the PTG trajectory should be used to extend the tested associations …...

**References**

Ai, L. A……

**Figure 1: Flowchart of Study Selection**

A screenshot of a flowchart

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**Table 1: Overview of the selected studies (k=21) for main analysis**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Source | Year | Sample size | Male,% | Age (mean) | End Point | Follow up, y | PTG Mean | PTG SD |
| Bluvstein et al. | 2013 | 82 | 60 % | 63.70 | Coronary heart disease | 6 months | 41.3 | 27.3 |
| Hu et al. | 2020 | 65 | 70.80% | N/A (>18) | Stroke | 3 months | 56.94 | 9.11 |
| Kearns et al. | 2020 | 304 | 65.5% | 65.5 | Cardiovascular diseases | ~12 months | 55.5 | 33.0 |
| Kelly et al. | 2017 | 43 | 58% | 74.53 | Stroke | 6 months | 51.53 | 26.25 |
| Leung et al. | 2012 | 2636 | 75% | 65.49 | Coronary artery disease | 1 year | 47.3 | 8.5 |
| Leung et al. | 2010 | 1497 | 71.30% | 65.98 | Coronary artery disease | 9 months | 50.3 | 27.2 |
| Losiak & Nikiel | 2014 | 53 | 60.37% | 57.30 | Myocardial infarction | ~5.5 weeks | 47.28 | 21.83 |
| Magid et al. | 2019 | 52 | 69.20% | 64.80 | Cardiac disease | 43 months | 35.25 | 15.93 |
| Maria et al. | 2021 | 44 | 100% | 63.26 | Myocardial infarction | N/A | 18.77 | 7.01 |
| Overbaugh et al. | 2017 | 103 | 76% | 74 | Heart failure | N/A | 48.6 | 28.6 |
| Rahimi et al. | 2016 | 166 | 84.9% | 55.3 | Myocardial infarction | ~7.78 months | 68.39 | 19.40 |
| Sheikh | 2004 | 110 | 79% | 63.5 | Heart disease | ~5 years | 55.85 | 24.19 |
| Aydındoğmuş, A., & Savaşan, A. | 2022 | 25 | 88% | 54.84 | Myocardial infarction | 3 months | 76.24 | 17.80 |
| De Oliveria et al. | 2023 | 63 | 65% | 65 | Heart failure |  | 67.02 | 13.26 |
| Gangstad & Norman et al. | 2009 | 60 | 56.67% | 71.67 | Stroke |  | 50.33 | 19.92 |
| Huang et al. | 2021 | 158 |  |  | Stroke | 3 months | 54.89 | 23.08 |
| Karagiorgou & Cullen | 2016 | 47 | 79% | 66.4 | Myocardial infarction |  | 54.6 | 23.6 |
| Kuenemund et al. | 2014 | 42 | 64% | 52.83 | Stroke | ~ 21 months | 57.69 | 19.28 |
| Ogińska-Bulik, N | 2014 | 86 | 72.10% | 60.50 | Myocardial infarction |  | 61.54 | 16.75 |
| Oginska-Bulik, N., & Gurowiec, P. J. | 2020 | 63 | 61.90% | 67 | Myocardial infarction |  | 37.05 | 17.67 |
| Peng, Z. Y., & Wan, L. H. | 2018 | 115 | 70.4% | 62.43 | Stroke | 6 months | 61.12 | 25.41 |

**Table 2: Statistical result of Main Analysis**

A table with numbers and symbols

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**Figure 2 : Forest Plot of Main Analysis**

A graph with numbers and lines

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**Table 3 :** Overview of the selected studies (k=13) for subgroup analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Source | Year | Sample size | Male,% | Age (mean) | End Point | Follow up, y | Determinant |
| Ai et al. | 2013 | 262 | 60% | 62.4 | Cardiovascular diseases | 2.5 years | Depression, Coping, Spirituality, Social Support, Age, Gender |
| Garnesfski et al. | 2008 | 139 | 82% | 35-70 | Myocardial infarction | 3~12 months | Depression, Coping, Spirituality, Age, Gender |
| Hu et al. | 2020 | 65 | 70.80% | N/A (>18) | Stroke | 1 month | Depression, Spirituality, Social Support |
| Javed & Dawood | 2016 | 90 | 58% | 45-65 | Myocardial infarction | 1 month – 3 years | Coping, Social Support |
| Kelly et al. | 2017 | 43 | 58% | 74.53 | Stroke | 6 months | Coping, Social Support |
| Losiak & Nikiel | 2014 | 53 | 60.37% | 57.30 | Myocardial infarction | ~5.5 weeks | Coping, Spirituality |
| Magid et al. | 2019 | 52 | 69.20% | 64.80 | Cardiac disease | 43 months | Coping, Age |
| Overbaugh et al. | 2014 | 103 | 76% | 74 | Heart failure | N/A | Age, Gender |
| Rahimi et al. | 2016 | 166 | 84.9% | 55.3 | Myocardial infarction | ~7.78 months | Social support |
| Sheikh | 2004 | 110 | 79% | 63.5 | Heart disease | ~5 years | Coping. Social Support |
| Senol-Durak & Ayvasik | 2010 | 132 | 11.4% | 52.04 | Myocardial infarction | N/A | Depression, Coping, Social Support, Age, Gender |
| Gangstad & Norman et al. | 2009 | 60 | 56.67% | 71.67 | Stroke |  | Depression, Coping |
| Peng, Z. Y., & Wan, L. H. | 2018 | 115 | 70.4% | 62.43 | Stroke | 6 months | Social Support |

**Table 4 : Results Summary of subgroup analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Correlate** | **K** | **N** | **ES** | **95% CI lower** | **95% CI upper** | **I2** |
| Depression | 5 | 658 | -0.15 | -0.41 | 0.11 | 91.96% |
| Coping Strategies | 9 | 941 | 0.50 | 0.33 | 0.66 | 93.04% |
| Spirituality | 4 | 519 | 0.56 | 0.38 | 0.75 | 89.38% |
| Social Support | 8 | 983 | 0.29 | -0.05 | 0.62 | 98.25% |
| Age | 5 | 688 | 0.04 | -0.12 | 0.20 | 78.49% |
| Gender | 4 | 636 | 0.10 | 0.03 | 0.18 | 11.01% |

**Appendix**

**Figure 3: Forest plot for Depression related PTG among COVID-19 people**

A graph with numbers and a line

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