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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)**

(01/01/2024, in Submission to Journal of The American Medical Association/JAMA)

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**A Meta-analytic Review**

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**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 (30), PsychINFO (6), Academic Search Complete (4 ), Ovid MEDLINE (20), electronic databases were systematically searched from May 23, 2023 through August 20, 2023 and an additional search was done until December 18, 2023, 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, posttraumatic growth, PTG, stress-related growth, adverse growth, positive outcomes, positive effects, self-growth. **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** The main outcome measure is PTGI. This includes variants of PTGI such as PTGI-SF and PTGI-X. All the scores collected were converted to regular PTGI scale so that we can effectively compare the results of the studies spanning more population. Such conversion makes our results more generalizable. In addition to PTGI, we also considered covariates that might influence PTG. The covariates can be categorized into two main types: 1) Major Risk Factors, and 2) Protective Factors. The major risk factor includes covariates such as depression, PTSD, and anxiety. Protective factors include covariates spanning from coping strategy to social support. **RESULTS** The search yielded 30 selected studies comprising 42, 386 participants of which 30 studies presented data on the COVID-19-PTG association, and 12 presented data on PTSD. On pooled analysis, COVID-19 induced a significantly positive PTG (g=0.75 95% CI [0.45, 1.05]), with a high heterogeneity in the analysis(*I*2=99.72%). Subgroup analyses indicated a slight association between Covid-19 related PTG and PTSD in COVID-19. For people who had PTSD, we obtained a mean effect size of g=1.04, 95% CI [0.07, 2.00]. For people who did not have PTSD, the mean effect size was g=0.55, 95% CI [0.18, 0.92].

**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).

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

**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 30 studies including 42, 386. 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.

**Introduction**

Since the World Health Organization declared the 2019 novel coronavirus (Covid-19) as a global emergency (Sohrabi et al., 2020), the pandemic has created a sweeping impact on mortality and detrimental psychiatric consequences (O’Connor et al., 2020; Wang et al., 2022). Unlike other severe diseases (e.g., cardiovascular diseases, cancer), Covid-19’s effect is pervasive and traumatic, influencing many sectors of populations (Krishnamoorthy et al., 2020) and at all levels (individual, family, community, nation, and the word). In medical settings, its highly contiguous nature also generatYed health and existential threats to both patients and health-care providers (Adjorlolo et al., 2022; Castiglioni et al., 2023; Chen et al., 2021; Khattab et al., 2020; Lewis et al., 2022; Yeung et al., 2022; Zhang et al., 2021).

Because of exposure to COVID-19, psychiatric stress and alter human cognition (e.g., negative thoughts or views of the world) could rise as do following other traumas (Moreland et al., 2023). However, positive cognition, such as posttraumatic growth (PTG), can also emerge with struggles as trauma-related psychological gains (e.g., positive mindset changes in cognition and worldview) (Calhoun & Tedeschi, 2006). Most observed domains of PTG involved greater positive changes in personal strength, appreciation of life, and social relationships. PTG is also a kind of better outcomes in patients with life-altering diseases (Ma et al., 2022; Pięta & Rzeszutek, 2022; Sawyer et al., 2010; Shand et al., 2015; Wang et al., 2022). A few meta-analyses have associated this phenomenon with low mortality in non-pandemic patients (Ma, Wan & Chen, 2022); Wan, Huang & Peng, 2023).

Given the long-term and vast impact of Covid-19 (Emek, et al., 2021; Parums, 2021), it is necessary to examine if PTG cooccur with this pandemic as a modifiable dimension of outcomes in the United States and globally. In 2021, a national representative study of US veterans reported moderate to greater levels of PTG resulting from the COVID-19 experience, especially among those suffering from posttraumatic stress symptoms (PTSD) linked with positive Covid-19 results (Pietrzak et al., 2021). Other studies have also shown the emergence of Covid-19-related PTG in the United States and other countries. To provide more reliable and robust conclusion on this positive worldview-based mindset change across different sectors of populations (general populations, health-care providers, and infected patients), we conducted this first meta-analytic review to examining PTG during and post COVID-19.

A meta-analyses on another pandemic has demonstrated the relationship between PTG and adjustment among individuals living with HIV/AIDS (Pięta & Rzeszutek, 2022). Yet, there is a lack of similar pooled analysis on the observed PTG in recent major pandemics. The paucity implies that more meta-analyses will be desirable for this optimal outcome in future medical research. Accordingly, this study employed a systematic approach to synthesize empirical studies in the United States and around the world. We aimed to reach a more creditable conclusion for an urgent question: Whether PTG could be observed globally under the threat of COVID-19 to mankind. More specifically, we evaluated the magnitude and consistency of the pandemic related PTG, as a change in posttraumatic positive cognition. We also conducted subgroup analyses linking PTG with certain risk and protective factors.

# **Methods**

# **Data Sources and Searches**

This systematic meta-analytic review was conducted and presented following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (Stroup et al., 2000). 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. 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, positive effects, positive outcome and self-growth. Furthermore, references from selected studies and relevant review articles were reviewed to identify additional publications (Cui et al., 2021; Feingold et al., 2022; Finstad et al., 2021; Hyun et al., 2021; Kowalski, Carroll & Britt, 2021; Li et al., 2022; Van der Hallen & Godor et al., 2022).

# **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, for the purpose of uniformity of measure, we decide to adopt PTGI (Posttraumatic Growth Inventory; Tedeschi & Calhoun, 1996) as the standard scale for measuring PTG. Any variants of PTGI such as PTGI-SF that could be easily converted to standard PTGI scale were included. Stated differently, only those with mean scores on PTG with standard deviation or correlates with PTG were included.

Studies using open-ended measures were also excluded due to the lack of validation. Studies that did not employ an established and validated scale that specifically focused on PTG, or used other types of measures for gains were excluded. Measures such as Stress-related growth scales (e.g., SRGS, Cohen, & Murch, 1996, Park & Blumberg, 2002) that were derived from a different set of items, and accesses different aspects of PTG, were excluded. The latter type of exclusion also involved measures on such broader positive changes as Benefit Finding Scale (Mohr et al. 1999) Perceived Benefit Scale (McMillen & Fisher, 1998). This was because certain gains did not pertain to adulthood growth.

**Data Extraction and Quality Assessment**

According to pre-planned protocol and using a standardized form, an assistant investigator (M.R.) 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 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, sex, COVID-19 diagnosis), PTG assessment tools, the measure of PTG in the form of PTGI, and the standard deviation of the measure for each study. The quality of the selected studies was assessed using Meta-analyses of Observational Studies in Epidemiology Checklist (Zuuren & Fedorowicz, 2016).

**Statistical Analysis**

R (version 4.3.1) was used to conduct the meta-analysis. The current study selected articles that reported the mean and standard deviation (SD) of Posttraumatic Growth (PTG) as assessed by the either Posttraumatic Growth Inventory (PTGI) developed by Tedeschi and Calhoun (1996) or its variants.

The PTG scale used in this study (PTGI) 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 below 45 indicated none to low levels of PTG, while scores of 45 or above indicated medium to high levels of PTG. This cutoff point was chosen based on its frequent usage in existing literature (Mazor et al, 2016; Naghavi et al, 2020; Taher & Allan, 2020; Wall et al, 2023).

The aforementioned 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. If we find that the PTG measure collected from the studies are significantly higher than 45 cut-off point, then we would conclude that, overall, across different population, among all different levels, PTG related to COVID-19 is significantly positive, and that people became stronger because of the global pandemic.

The current study uses a random effect meta-analytical model for main analysis. Random effect model does not assume a single true effect size, but rather assume a distribution of true effect sizes. This allows us the flexibility to take the between-study variability/heterogeneity in effect sizes into account in this analysis.

**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 60 unique publications, of which 42 qualified for full-text review. In the end, 30 studies (Adjorlolo et al., 2022; Arnout & Al-Sufyani, 2021; Bai et al., 2023; Barnicot et al., 2023; Castiglioni et al., 2023; Chasson et al., 2022; Chen & Tang, 2021; Chen et al., 2020; Das et al., 2023; El-Khoury Malhame et al., 2023; Gul et al., 2023; Kalaitzaki, Tsouvelas & Tamiolaki, 2022; Kalaitzaki et al., 2023 ; Lan et al., 202; Lau, Chan & Ng, 2021; Lewis et al., 2022; Lyu et al., 2021; Morales et al., 2023; Mo et al., 2022; Northfield & Johnston, 2021; Tu et al., 2023; Ulset & von Soest, 2022; Vazquez et al., 2021; Wang et al., 2023; Willey et al., 2022; Yao et al., 2023; Yeung et al., 2022; Yildiz, 2021; Zhang et al., 2021; Zhou, MacGeorge & Myrick, 2020), met the inclusion criteria for the main analysis. 12 studies were selected for subgroup analyses on PTSD citations of them (Arnout & Al-Sufyani, 2021; Chen & Tang, 2021; Chen et al., 2020; Das et al., 2023; El-Khoury Malhame et al., 2023; Lan et al., 2023; Lau, Chan & Ng, 2021; Lewis et al., 2022; Mo et al., 2022; Vazquez et al., 2021; Wang et al., 2023; Zhang et al., 2021). Of these 12 included in the analysis, all employed PTGI or its variants (e.g. PTGI-SF) to examine PTG. Nineteen were cross-sectional studies and 7 were prospective studies. For the selected studies involving a total of 42,386 individuals, table 1 and table 3 present their overall characteristics.

Among the studies included in the analysis, seven studies were performed in the United States (Chen et al., 2021; Morales et al., 2023; Northfield & Johnston, 2021; Tu et al., 2023; Willey et al., 2022; Zhang et al., 2021; Zhou, MacGeorge & Myrick, 2020), two in the United Kingdom (Barnicot et al., 2023; Lewis et al., 2022), one in Ghana (Adjorlolo et al., 2022), two from Greece (Kalaitzaki et al., 2022; Kalaitzaki et al., 2023) and from the European countries of Norway, Italy and Spain one study was found in each (Castiglioni et al., 2023; Vazquez et al., 2021; Ulset & von Soest, 2022) five from the Middle Eastern countries of Turkey, Pakistan and Saudi Arabia, and Israel (Arnout & Al-Sufyani, 2021; Chasson et al., 2022; Das et al., 2023; El-Khoury Malhame et al., 2023; Gul et al., 2023; Yildiz, 2021), nine from China, (Bai et al., 2023; Chen & Tang, 2021; Lan et al., 2023; Lau et al.,, 2021; Lyu et al., 2021; Mo et al., 2022; Wang et al., 2023; Yao et al., 2023; Yeung et al., 2022). Included articles involved a variety of different types of people such as patients and the general population (Adjorlolo et al., 2022; Arnout & Al-Sufyani, 2021; Castiglioni et al., 2023; Chen & Tang, 2021; El-Khoury Malhame et al., 2023; Gul et al., 2023; Kalaitzaki et al., 2022; Lau, Chan & Ng, 2021; Lewis et al., 2022; Northfield & Johnston, 2021; Ulset & von Soest, 2022; Vazquez et al., 2021; Willey et al., 2022; Zhou et al., 2020), nurses and medical doctors (Bai et al., 2023; Barnicot et al., 2023; Chen et al., 2020; Das et al., 2023; Kalaitzaki et al., 2023; Lyu et al., 2021; Mo et al., 2022; Yao et al., 2023; Yeung et al., 2022; Zhang et al., 2021), pregnant women (Chasson et al., 2022), and students (Lan et al., 2023; Morales et al., 2023; Tu et al., 2023; Wang et al., 2023; Yildiz, 2021) most of which centered on the general population during COVID 19.

**Main analysis**

The main analysis included 30 studies involving a total of 42,386. The sample size of these studies ranged from 100 (Willey et al., 2022) to 12,586 individuals (Ulset & von Soest, 2022). Most of the studies had a significant proportion of male participants, with the percentage ranging from 4.40% (Chen et al., 2020) to 61.62% (Das et al., 2023); Mean age of them ranged from age of 24.96 (Zhai et al., 2021) to age of 76.3 (Willey et al., 2022). 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 (Arnout & Al-Sufyani, 2021; Gul, 2023; Morales et al., 2023).

The mean PTG ranged from 26.54 to 98.30 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. The main analysis revealed a significant positive effect relative to the cutoff point of 45. The hedges’ g calculated to reflect the deviation from the 45 cutoff points is 0.75 with 95% CI [0.45, 1.05]. Based on the rule of thumb, 0.5 shows a medium effect and 0.8 or above presents a large effect (Taylor & Alanazi, 2023). This results indicated a highly positive relationship of PTG to COVID-19. I2 value 99.72% in table 3 also high heterogeneity among selected studies.

**Subgroup Analyses of PTG and Covariates**

Table 4 shows the summary of subgroup analyses. The ?? selected studies included such variables as determinants of PTG (i.e., PTSD/PTSS, depression/anxiety, social support, ???, coping??, spirituality??, age and gender).

***PTSD/PTSS***

Twelve selected studies presented the association of PTSD with PTG with a total of 19774 participants (Arnout & Al-Sufyani, 2021; Chen & Tang, 2021; Chen et al., 2020; Das et al., 2023; El-Khoury Malhame et al., 2023; Lan et al., 2023; Lau, Chan & Ng, 2021; Lewis et al., 2022; Mo et al., 2022; Vazquez et al., 2021; Wang et al., 2023; Zhang et al., 2021). The baseline effect size (the intercept term) is g=0.55, and whether the studies investigated PTSD yielded a higher effect with the regression coefficient associated with the PTSD term being *B*=0.49. However, PTSD as a moderator is not significant (*p*-value=0.11). Thus, we conclude that there exists no significant relationship between PTSD and PTG but the broad range indicates a considerable amount of uncertainty in the effect estimate (*SE*=0.30). An I2 value of 99.60% showed substantial heterogeneity across the studies.

***Mental Health* (*Depression, Anxeity*)**

Twelve (??) selected studies presented the association of depression with PTG with a total of ??? participants (Barnicat et al., 2023; Castiglioni et al,, 2023; Chen et al., 2021; Cohen et al., 2023; Finstad et al., 2021; Park & Im, 2021; Sim & Im, 2023; Ulset & Soest, 2021; Vazquez et al., 2021; Xiao et al., 2022; Zhai et al., 2021; Zhen et al., 2022; Zhou et al., 2020??).The pooled effect size of -0.15[-0.41,0.11] was consistent with there being no (??) relationship between depression and PTG but the broad range indicates considerable uncertainty in the effect estimate. A high I2 value of 91.96% showed substantial heterogeneity across these studies.

***Social Support*** (just on e All protective fac will depend on your final selection, not settled yet)

(Lewis et al., 2022; Mo et al., 2022; Northjfield & Johnston, 2022; Zhai et al., 2021; Zhang et al., 2021)

***Coping***

(Dominick & Elarn, 2023; Kalaitzaki et al., 2021; 2021;) Please redo in a very precise way: Various types of coping strategies were investigated with PTG in nine studies. Ai et al.16, Gangstad et al.51 and Kelly et al.38 focused on active coping strategies, while Łosiak and Nikiel 30 and Garnesfski et al.28 delved into cognitive coping strategies. Senol-Durak and Ayvasik 31 investigated "cognitive process coping," and Magid et al.57 explored coping strategies associated with alterations in cognition and mood. Furthermore, Javed and Dawood 36 examined active emotional coping, problem-focused coping, and avoidant coping, and Sheikh 22 discussed both problem-focused and emotion-focused coping. Building on these findings, an average was calculated from the results presented by these two papers which contain multiple coping strategies since their correlation are close to each other.22,36 Figure 4 shows the role of coping in PTG, assessed in the cited studies which collectively encompassed 941 participants.16,22,28,30,31,36,38,51,57 The pooled effect size yielded a value of 0.50[0.33,0.66], denoting a positive association between coping mechanisms and the degree of PTG (table 4). However, a significant level of heterogeneity across the examined studies was revealed due to the high I2 statistic of 93.04%.

***Spirituality***

(Dwiwardani etal., 2022; Prieto-Ursua & Jodar, 2020; Yeung et al., 2022) Regarding spirituality, four studies were considered, involving a total of 519 participants.16,28,30,52 As shown in Figure 5, a moderately-high positive relationship was discerned between spirituality and PTG, as highlighted by an effect size of 0.56[0.38,0.75]. ……

**Discussion**

To our knowledge, this study is the first meta-analysis to estimate the relationship between Covid-19 and PTG. Overall, across a diverse population in different parts of the world, people facing the global pandemic demonstrated resilience and growth, coming out of the pandemic stronger. This finding lends strong support for s our primary hypothesis.The current review has provided compelling findings for PTG, associated with the Covid-19 pandemic that imposed existential crisis around the world over three years since late 2019. Selected studies cover strong evidence from research conducted the United States and beyond, which involving patients, health care providers, students, veterans, and general populations from four continents. Our findings suggest that this positive outcome can emerge from deadly diseases with a global scope, as was shown in other chronic ailments with certain life risks (Ma et al., 2022; Pięta & Rzeszutek, 2022; Sawyer et al., 2010; Shand et al., 2015; Wang et al., 2022). Different from those conditions, Covid-19 took lives of nurses and physicians who provided direct or indirect services of patients who were infected.

This meta-analysis consisted of 30 studies(Adjorlolo et al., 2022); (Arnout & Al-Sufyani., 2021); (Bai et al., 2023); (Barnicot et al., 2023); (Castiglioni et al., 2023); (Chasson et al., 2022); (Chen & Tang., 2021); (Das et al., 2023); (El-Khoury Malhame et al., 2023); (Gul et al., 2023); (Kalaitzaki, Tsouvelas & Tamiolaki, 2022); (Kalaitzaki et al., 2023); (Lan et al., 2023); (Lau, Chan & Ng, 2021); (Lewis et al., 2022); (Lyu et al., 2021); (Morales et al., 2023); (Mo et al., 2022); (Northfield & Johnston, 2021); (Tu et al., 2023); (Ulset & von Soest, 2022); (Vazquez et al., 2022); (Wang et al., 2023); (Willey et al., 2022); (Yao et al., 2023); (Yeung et al., 2022); (Yildiz, 2021); (Zhang et al., 2021); (Zhou, MacGeorge & Myrick, 2020) involving 42,386…. participants. All of them associated PTG with Covid-19. # of studies also associated PTG with ..???? (QZ). Despite the heterogeneity in sample characteristics (e.g., age, country of origin, culture, position in the pandemic), the result among studies were consistent. An overall pooled risk ratio of….. suggests…….(QZ). Of 30 studies, ??# of them showed whatever….(need just key # here to make your statement! (QZ)

**Clinical Significance**

The pooled international evidence pointed to three potential directions for future pandemic health care and investigation. First, this systematic review involves considerable variability in study samples, global locations, age range, and cultural diversity. The consistent results, however, suggests that the PTGI may be an suitable instrument for assessing this positive outcome following the similar catastrophe. Further longitudinal research might provide more information for its application as a clinical tool in medical settings.

Second, Covid-19 and similar deadly pandemics may cause remarkable population impact and long-term health damage in certain proportions of patients (e.g., long-Covid). Whether PTG will be related to the better prognosis of pathological process of Covid-19 and a survival benefit for victims of long Covid-19 remains unknown. However, a meta-analysis showed its association with low mortality in non-pandemic patients (Ma, Wan & Chen, 2022); Wan, Huang & Peng, 2023). If this is the case for people affected by pandemics, the development of PTG-enhancing interventions benefit patients and high-risk care providers.

Finally, PTG and pathology belong to two different paradigms in human wellbeing (Ai et al., 2013; 2021), while PTG and PTSD are both related to struggle as two sides for one coin, trauma. Beyond PTG-related psycho-behavioral theories, a new study also suggested the complicated mechanisms involving many domains (e.g., physiological, biochemical, immunological, neuronal, and genetic alteration (Dell’Osso et al., 2023). More interdisciplinary studies are warranted in this regard to better inform clinical medicine.

**Mechanisms**

Most studies in this meta-analysis did not involve basic science investigation, but evidence has emerged in the past decade. In the neuroendocrine and immunological area, Smyth et al. (2008) and Diaz et al. (2014) have assorted higher levels of PTG with low levels of cortisol in patients suffering from PTSD and women with breast cancer, respectively. In the brain function and structures area, Rabe et al. (2006) linked PTG with the frontocentral EEG alpha asymmetry in survivors of motor vehicle accidents, controlling for trait positive affect. Importantly, one unique study positively associated PTSS during Covid-19 with grey matter volume in medial prefrontal cortex/dorsal anterior singular cortex in structured magnetic resonance imaging data acquired before the pandemic(Lan et al., 2023). However, PTG was negatively correlated with grey matter volume in left dorsolateral prefrontal cortex.

In the genomic area, Dunn et al. (2014) pioneered the gene-environment (GxE) interaction study in relation to PTG using a New Orleans sample of low-income non-Hispanic Black individuals who exposed to Hurricane Katrina. Among the identified ten common variants in seven genes, the presence of homozygotes rs4606 variants of RGS2 gene was strongly associated with greater PTG after multiple testing, which appeared to be driven by a GxE interaction. Finally, in the cardiac physiology area, Wei et al. (2017) found that, in posttraumatic individuals who responded to positive images, the low and high frequency components of HRV were significantly higher in PTG group than in control and PTSD group. Clearly, basic science research of PTG in Covid-19 may assist better understanding of its medical implications.

**Limitations**

The limitations of this meta-analysis should be acknowledged. First, methodological heterogeneous exist across studies and contributed to divergent findings of studies included. The diverse populations involved, concerning age, race, cultural, geographic location, and roles in the pandemic (e.g., patients, health providers, general populations) may also lead to heterogeneous findings. The link between Covid-19 and PTG was nevertheless evident across these studies. Second, to be conceptually sound, we excluded studies with scales without specific foci on growth and those with only unvalidated, single-item measures. This decision could exclude potentially valuable information. Third, important medical indices are missing in most studies; thus, we could not systematically assess their associations with PTG. Fourth, covariates included in studies vary wildly, which may account for the heterogeneity in our subgroup analysis. Finally, due to the emergent pandemic, studies in this meta-analysis were published in a close period (2020-2022) with few were conducted in a prospective design. The increased overtime growth has been observed by a new Covid-19 (Kalaitzaki et al., 2023) and a few non-Covid (Ai et al., 2021; Hu et al., 2020; Kelly et al., 2018) prospective studies, a fact underscoring the need to follow-up post-pandemic PTG.

**Conclusions**

Over the past two decades, burgeoning research has shown PTG as a promising endpoint after trauma and disasters. The findings from this first meta-analysis suggest that the optimal outcome could occur among patients, health care providers, and general populations who were all exposed to the Covid-19 threat globally. PTG includes a posttraumatic worldview change in varied domains, or positive outlook, that could lead to optimal behavioral changes. Future research should employ prospective designs to reveal its health benefit in long-term survival and quality of life. Investigation should also address important medical questions (e.g., What could be behavioral and salutogenic mechanism of adulthood growth to inform potential interventions.

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**Figure 1: Flowchart of Study Selection**

Studies from databases/registers (n=60)

**Identification**

Duplicates removed. (n=10)

Records screened.

(n=42)

Records excluded\*\*

(n=30)

Reports not retrieved.

(n =0)

Reports sought for retrieval.

(n=35)

**Screening**

Reports excluded:

(n=30)

Wrong scale: (n= 10)

Reports assessed for eligibility.

(n=35)

Studies included in review.

(n=30)

**Included**

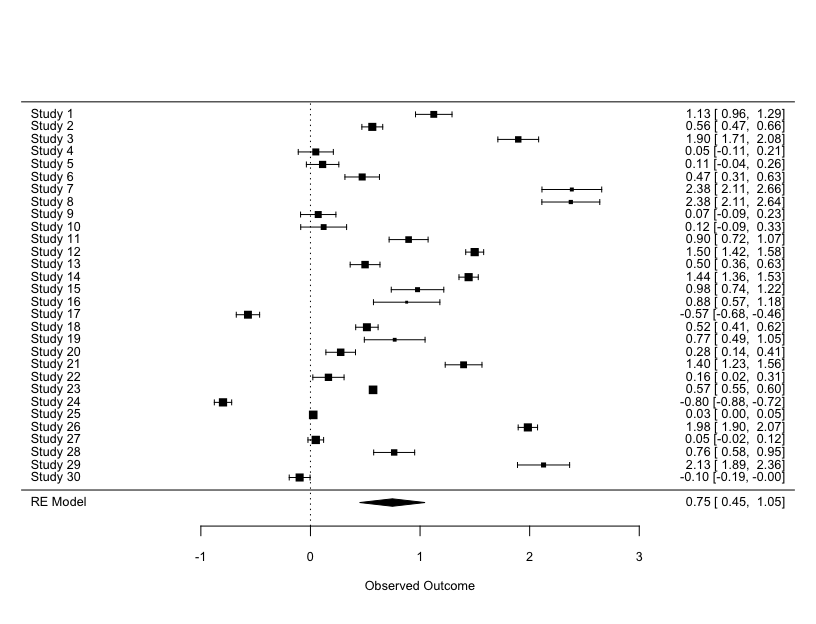
**Table 1: Overview of the selected studies (k=30) for main analysis**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Source | Year | Sample Size | Male % | | Age (Mean) | | Endpoint | | Follow up, y | | PTG Mean | PTG SD | |
| Adjorlolo et al. | 2022 | 381 |  | 59.3 | | 43.1 | |  | | 3-months | | |  |
| Arnout & Al-Sufyani | 2021 | 365 |  | 31.8 | | n/a | |  | | n/a | | |  |
| Chasson et al. | 2022 | 916 |  | n/a | | 28.16 | |  | | n/a | | |  |
| Chen & Tang | 2021 | 476 |  | 55.50 | | 32.7 | |  | | January 20th | | |  |
| Chen et al. | 2020 | 12,596 |  | 4.40 | | 32.7 | |  | | n/a | | |  |
| Das et al. | 2023 | 166 |  | 61.62 | | 36.7 | |  | | n/a | | |  |
| Dominick & Elam | 2023 | 201 |  | 22.40 | | 35.39 | |  | | 4/30/20-9/30/20 | | |  |
| El-Khoury Malhame et al. | 2023 | 252 |  | 71(28.3) | | 25.00 | |  | | n/a | | |  |
| Gul | 2023 | 300 |  | 50 | | n/a | |  | | n/a | | |  |
| Kalaitzaki et al. | 2022 | 1,361 |  | 24.2,17.3 | | 35.36 | |  | | Second Lockdown | | |  |
| Lan et al. | 2023 | 115 |  | 49 | | 22.37 | |  | | February-April 2020 | | |  |
| Lau et al. | 2021 | 327 |  | 28.10 | | 35 | |  | | 4/24/20-5/12/20 | | |  |
| Lewis et al. | 2022 | 1,424 |  | 21.90 | | 46.7 | |  | | November 20th | | |  |
| Lyu et al. | 2021 | 535 |  | 45.79 | | 35.41 | |  | | May 20th | | |  |
| Mo | 2022 | 266 |  | 24 | | 32.34 | |  | | n/a | | |  |
| Morales et al. | 2023 | 891 |  | 310 | | n/a | |  | | n/a | | |  |
| Northfield & Johnston | 2021 | 296 |  | 41.20 | | 39.7 | |  | | n/a | | |  |
| Pietrzak et al. | 2021 | 7,860 |  | 91.60 | | 63.3 | |  | | 11/9/20-12/19/20 | | |  |
| Prieto-Ursua & Jodar | 2020 | 1,091 |  | 30.60 | | n/a | |  | | n/a | | |  |
| Tu et al. | 2023 | 290 |  | 123 | | 25-29 | |  | | n/a | | |  |
| Ulset & Soest | 2022 | 12,686 |  | 43.6 | | n/a | |  | | n/a | | |  |
| Vazquez et al. | 2021 | 1,951 |  | 918 | | 45.16 | |  | | n/a | | |  |
| Wang et al. | 2023 | 100 |  | n/a | | 22.42 | |  | | n/a | | |  |
| Willey et al. | 2022 | 176 |  | 74 | | 76.3 | |  | | n/a | | |  |
| Yao et al. | 2023 | 1,512 |  | 6.20 | | 32.46 | |  | | n/a | | |  |
| Yeung et al. | 2022 | 1,510 |  | n/a | | 36.8 | |  | | September 20th | | |  |
| Yildiz | 2021 | 292 |  | 63 | | 21.20 | |  | | n/a | | |  |
| Zhai et al. | 2021 | 423 |  | 157 | | 24.96 | |  | | n/a | | |  |
| Zhang et al. | 2021 | 1,790 |  | 11 | | n/a | |  | | n/a | | |  |
| Zhou et al. | 2020 | 1,021 |  | 47.31 | | 45.3 | |  | | 5/4-5/8, 5/18-5/22 | | |  |

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Random Effects Model (k=30)** | |  |  |  |  |  |  |
|  | Estimate | se | Z | p | CI Lower Bound | CI Upper Bound |  |
| Intercept | 0.75 | 0.15 | 4.92 | <.0001 | 0.45 | 1.05 |  |
| Heterogeneity Statistics | |  |  |  |  |  |  |
|  | Tau | Tau^2 | I^2 | H^2 | df | Q | p |
|  | 0.83 | 0.69 | 99.72% | 352.96 | 29 | 6174.90 | <.0001 |

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

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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

Description automatically generated

**Methodological Heterogeneity across Studies**

In the final sample of studies, most studies used PTGI or its variations (e.g., SF, CPTGI), except one used SRGS-SF (Zhai et al., 2021). Despite the discrepancy in assessments, the link between CVD and PTG were compatible among studies. Thus, both scales on adulthood growth should be seen as usable in Covid-19 research. Given its wide usage in international studies, PTGI should be considered as a better choice in future clinical studies. Furthermore, the… For example, mean age of Chasson et al.’s (2022) study was 28.16, whereas Pietrzak et al.’ (2021) was 63.3. Both groups showed moderate or moderately high-level PTG (this may be modified based on subgroup analysis of age effects). Finally,

This diverse populations in these studies concerning age, race, cultural, and roles in the pandemic (e.g., patients, health providers, general populations). There was also the variation in when PTG was observed across 30 studies. The assessment time ranged from ?? month (?? et al., 202?) to?? years (?? et al., 202? QZ, replace them). Fifth, some studies did not specify the gender positively related to PTG. Sixth, Given the complicated relationship of PTG with PTSD and depression, two CVD mortality risks, it should be interesting to explore the likely intertwining trajectory of the three constructs in patients with CVD prognosis. Finally, we do not have enough effect size to test a PTG-PTSD relationship in PTG. …Most studies are cross-sectional in nature, hindering the statement of causality, even though and a cross-sectional design was included in previous meta-analyses (e.g., Stroup et al., 2000).

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