The Impact of Covid-19 on Cognitive Function in Recovered Patients: A Meta-Analysis

Mercedes Mudgway

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Abstract

Covid-19 is associated with cognitive impairment despite resolution of the acute infection. Our objective was to conduct a meta-analysis to quantify the proportion of individuals experiencing cognitive impairment after recovering from Covid-19. We performed a literature search completed on 31 August 2021, based on our pre-registered PRISMA protocol. Searches were conducted without language restrictions on Google Scholar, PsychINFO, Scopus, PubMed, Science Direct, Web of Science, and ProQuest Dissertations & Theses Global. Primary research articles which evaluated individuals with a negative PCR test after recovery from confirmed Covid-19 diagnosis and specifically reported cognitive impairment were selected. One reviewer independently extracted published data and assessed methodological quality and risk of bias. A meta-analysis was conducted using the random-effects model. The primary outcomes were the proportions of individuals reporting cognitive impairment after recovering from Covid-19 infection. The literature search yielded 79,200, excluding duplicates, and ten studies were selected for inclusion. The meta-analysis revealed cognitive impairment in individuals recovered from Covid-19 with an effect of g = -.53, 95% CI [-0.75, -0.31], p = 0.0000019, k = 10, I^2 = 57.69%. We included various moderating variables, including race/ethnicity, regional differences, sex, age, disease severity, strain variants, genetic variants, treatments and comorbidities. These results indicated a proportion of individuals experience cognitive impairment after recovering from Covid-19. The frequency and nature of the prevailing symptoms indicate the need for more studies with larger samples and control groups to understand the underlying mechanisms that cause cognitive impairment.

Dedication

I dedicate this work to my dad for always believing, encouraging, and guiding me. I would not be in this position without you. Thank you.

Acknowledgements

I would like to thank my other half Matt for always supporting me, even when you had no idea what I was talking about. To our pupperino Billy for always giving me cuddles when I was anxious. To my family and friends, the best people when I needed to relieve some tension and have normalcy during a time of high stress - thank you all. Lastly, I would like to acknowledge my supervisor, Dr David Moreau; your expertise has been invaluable in completing my work.

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CHAPTER 1: INTRODUCTION

Coronavirus disease 2019 (Covid-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2), has rapidly spread throughout the world and continues to infect millions of people. Symptoms of Covid-19 are primarily systemic or respiratory and include fever, dry cough, fatigue, and dyspnea (Baj et al., 2020). Covid-19 was first identified as a respiratory syndrome, with some patients developing pneumonia (Hsu et al., 2021; Lai et al., 2020), which in some cases would progress to critical complications such as acute respiratory distress syndrome (ARDS) (Hsu et al., 2021; Lai et al., 2020), septic shock (Kazory et al., 2020), and multiple organ failure (Evans et al., 2021). As research progresses, it is becoming evident that long-term health problems, including neurological symptoms such as headache, altered consciousness, memory loss, and confusion, are associated with post-Covid-19 infection (Varatharaj et al., 2020). Coronaviruses are defined as enveloped viruses containing a single-stranded ribonucleic acid (RNA) (Pal et al., 2020) and are characterised as zoonotic due to their ability to transfer from animals to humans (Pal et al., 2020).

Human coronaviruses are known to target the CNS and cause damage by direct neurotoxicity or activation of the host immune response (Miners et al., 2020). Early research suggests that the neurological manifestations of Covid-19 can be considered a direct effect of the virus's capability of invading the CNS (Mao et al., 2020; Nuzzo & Picone, 2020). The impact that viral CNS infection and inflammatory processes have on cognitive functions is widely documented and, in some instances, can lead to transient or permanent cognitive impairment (Almeria et al., 2020; Bohmwald et al., 2021; Ritchie & Chan, 2021; Sartori et al., 2012). Research has suggested that the temporal regions appear to be a consistent focus for cognitive impairment (Ritchie et al., 2020). Some have suggested that the limbic system and associated brain structures such as the basal ganglia and hippocampus contain more enzymes involved in inflammatory response than other areas, which might mediate the

increased risk of developing deficits in neurocognitive processes like memory, attention, and emotion (Raz & Rodrigue, 2006; Sartori et al., 2012). However, other research indicates abnormal findings in the frontal lobe, occipital lobe, insular cortex, and cingulate gyrus (Kandemirli et al., 2020), as well as white matter changes (Bougakov et al., 2021; Hampshire et al., 2021; Paterson et al., 2020), and encephalopathy (Bougakov et al., 2021). These findings suggest that Covid-19's impact on the brain could be multifaceted, and the extent of post-Covid-19 cognitive impairment will likely be vastly heterogeneous, depending on the underlying pathophysiological mechanisms (Kumar et al., 2021). The observed cognitive impairment after Covid-19 has prompted a recent wave of publications.

There is growing evidence that individuals who have recovered from Covid-19 demonstrate manifestations of impairments in memory, attention, and executive function (Alnefeesi et al., 2020; Hampshire et al., 2021), with reports of delirium, systemic inflammation, and evidence of neurotropism (Baker et al., 2021). The differences in the incidence and the severity of cognitive dysfunction of individuals are likely to be multifaceted, depending on various biological, social, and economic factors (Moghimi et al., 2021). Since the pandemic's beginning, researchers have relied on various methods to understand the degree to which Covid-19 has implicated cognitive function. Population, cross-sectional, and longitudinal cohort studies have proven to be the most popular. They include samples of individuals from different racial-ethnic groups, sex, age, as well as varying comorbidities and severity of Covid-19 infection. The use of these inclusive samples offers insight into the variability of the cognitive impairment that patients may encounter after recovering from the virus. However, it is difficult to assess the overall consistency between Covid-19 and cognitive function. The present registered meta-analysis investigation aims to contribute to the literature by examining the role of Covid-19 on cognitive function to build a more systematic understanding of Covid-19 and the moderating variables of Covid-19

on cognitive function. We begin with an introduction of the current research on Covid-19 and cognitive function, including a theoretical account of how Covid-19 might impact cognitive function, followed by a discussion of empirical findings in this field, as well as possible moderators, and then proceed to report the methods and findings of our pre-registered meta-analysis.

Covid-19 and Cognitive Function

One of the most notable studies in Covid-19 and cognitive function was conducted by (Zhou et al., 2020). At the time of writing, there were 134 citations of the article and many important follow-up theoretical and empirical articles, notably Butler et al. (2020), Ferrucci et al. (2021), Graham et al. (2021) and Mazza et al. (2021). In the study conducted by (Zhou et al., 2020), a within-subject design was used for a clinical population and a control group of college students in Zhejiang, China. The study was conducted in a hospital environment under specific inclusion criteria to measure the cognitive function of individuals who had recovered from Covid-19. The participants undertook neuropsychological tests conducted by trained psychiatrists. The neuropsychological assessments generated measures of cognitive function in several cognitive domains. The results demonstrated that patients who had recovered from Covid-19 exhibited cognitive dysfunction in the sustained attention domain. Follow-up studies found that persistent “brain fog” (Graham et al., 2021), executive function impairment, psychomotor coordination impairment (Mazza et al., 2021), slowed cognitive processing speed, slowed short-term verbal and spatial memory dysfunctions (Ferrucci et al., 2021), symptoms that are often referred to as Long Covid were consistent in recovered Covid-19 patients.

Moderators

Research on the effects of Covid-19 and its impact on cognition is in its infancy. Establishing whether the relationship differs across participants' characteristics and clinical characteristics will help inform further research and who may benefit from interventions to enhance cognition after recovering from Covid-19. We tested the effects of four pre-registered moderating variables relative to participants: race/ethnicity, regional differences, sex, and age. Further, we tested the effects of four pre-registered moderating variables relative to clinical characteristics: disease severity, strain variants, genetic variants, and treatments.

Moderators in Participant Characteristics

Race/ethnicity was examined as a moderator of outcome disparities in early Covid-19 research. Current data on racial and ethnic minority groups suggest a disproportionate burden of death and illness from Covid-19 (Jain et al., 2020). Factors that influence ethnic and racial minority group health includes social and economic conditions (Sze et al., 2020), inability to access healthcare (Sze et al., 2020; Vasquez Reyes, 2020), racial residential segregation, and living in densely populated areas that hinder the principles of social distancing (Jain et al., 2020). Analysing the disproportionate affliction of Covid-19 on racial-ethnic minorities is essential to determine health outcomes (Vasquez Reyes, 2020). It has been suggested that racial-ethnic minority groups are strong and significant predictors of infection burden (Gale et al., 2016), suggesting a higher prevalence of viruses (Zajacova et al., 2009) and cognitive impairment (Smith et al., 2012). We predicted that Covid-19 would positively correlate between cognitive impairment and racial-ethnic groups in line with this research.

Regional differences refer to the location where individuals live in their everyday lives. We examined regional differences as a moderator to identify whether higher rates of cognitive impairment from Covid-19 were associated with a patient's location. Research

suggests that Covid-19 hospitalisation and mortality rates are higher in more deprived areas (Batty et al., 2020); however, the mechanisms that underlie these differences are complex and multifaceted. For example, nutritional factors, unhygienic conditions, poor community hygiene, and close living conditions may contribute to higher rates of Covid-19 (Jain et al., 2020). Early research suggests environmental factors, such as humidity and heat, are correlated with daily counts of Covid-19 cases (Qi et al., 2020). To the best of our knowledge, whether regional differences influence the relationship between Covid-19 and cognitive function had not been investigated. Therefore, we did not make specific predictions about how regional differences will impact cognition.

We examined sex as a moderator to measure whether impairment of cognitive function from Covid-19 differs between sexes. Being male has emerged as an independent risk factor for the poor prognosis from Covid-19 infection after suggestions that men produce more severe symptoms and higher mortality than women (Park, 2020; Ursin & Klein, 2021). Epidemiological research on coronaviruses indicates that males show a greater severity of infection (Okwan-Duodu et al., 2021). Current data on sex differences suggest male bias in Covid-19 mortality is observed in nearly all countries where data is available, with the risk of death in males approximately 1.7 times higher than in females (Takahashi & Iwasaki, 2021). Current research on respiratory viral infections indicates that during reproductive years (i.e., after puberty and before menopause in females), females often experience worse outcomes than males (Ursin & Klein, 2021). Which could be partially explained by immunological changes associated with pregnancy and reproduction (Ursin & Klein, 2021). Given this mixed evidence, we could not make a specific prediction as to how Covid-19 and cognitive impairment are influenced by sex.

We examined age as a moderator to measure differences in cognitive function across varying age groups. Cognitive changes continue to occur throughout the adult life span, and

as some abilities improve or remain steady, others decline (Mather, 2010). Current research shows that Covid-19 disproportionately affects older people; this is the group most likely to require hospital admission and are most likely to die from Covid-19 infection (De Biase et al., 2020). Age is a well-known risk factor for infection; however, why Covid-19 is particularly dangerous in older people is poorly understood (Mueller et al., 2020). Older adults are more susceptible to altered mental states (O'Hanlon & Inouye, 2020) and high in-hospital mortality, independent of pre-existing medical conditions and measures of disease severity (Marengoni et al., 2020). As a result, we predicted that age is a reliable predictor of the severity and variability of cognitive dysfunction from Covid-19.

Moderators in Clinical Characteristics

Disease severity refers to the hierarchy of Covid-19 symptoms (National Institute of Health, 2021). The severity of Covid-19 is highly heterogeneous, and predictive features of disease severity are associated with several factors, including comorbidities, race/ethnicity, age, and sex (Booth et al., 2021; Thakur et al., 2021). Research suggests that Covid-19 can be associated with ARDS, neurologic syndromes, and cardiac events (Pfortmueller et al., 2020). It has been suggested that viruses contribute to cognitive deficits due to the body being exposed to pathogens (Mawanda & Wallace, 2013; Ritchie et al., 2020; Strandberg et al., 2003; Tarter et al., 2014). These results are consistent with prior studies which have identified an association between chronic infections and cognition (Calsavara et al., 2018; Gale et al., 2016; Shah et al., 2013). The pattern of cognitive deficits among patients with Covid-19 shows the correlation of severity and cognitive dysfunction, suggesting a pattern of cognitive deficit among patients with mild to severe Covid-19 (Beaud et al., 2021; Miskowiak et al., 2021). Given this evidence, we predicted that disease severity does not indicate cognitive deficits.

Strain variants refer to the changes that occur at the biological level of a virus' genetic properties (Lauring & Hodcroft, 2021). Viruses mutate to survive within their environment, and these changes can affect how the virus spreads, vaccine performance, treatments, associated disease severity, and other social measures and public health (Jamil et al., 2021; Kupferschmidt, 2021; Leung, 2021). The emergence of variants can be of significant risk to public health. Specifically, mutations may detrimentally change Covid-19 epidemiology, enhance virulence, increase transmissibility rates, or change clinical disease presentation (Nikhra & Others, 2021; Otto et al., 2021; Williams et al., 2021). Preliminary data on Covid-19 indicate that some variants could be associated with more severe disease (Frampton et al., 2021); however, there is limited research on whether strain variants alter the severity of post-Covid-19 cognitive impairment. Therefore, we did not make specific predictions about how strain variants impact cognition.

Genetic variants refer to human genetic influence on infectious disease susceptibility (Kwok et al., 2021). It is suggested that genetic variants of a host are important contributors to variability in immune responses and outcomes of respiratory viral infections (Ursin & Klein, 2021). Multiple genetic factors are involved in Covid-19 severity and susceptibility. In general, proteins engaged in the viral life cycle and host defence pathways are essential genetic factors (Chakravarty, 2021). While genetic variants may contribute to clinical differences in Covid-19 pathogenesis, we are not aware that these variants affect cognition after viral infection. Therefore, we did not make specific predictions about how genetic variants impact cognition.

Treatment refers to a procedure or other action to prevent or manage disease or improve health (Rakel, 2021). Treatment strategies for Covid-19 are being developed at an accelerated rate for both therapeutic and preventative therapies (Kim et al., 2020; LaVange et al., 2021; Xiao et al., 2020). For example, pharmacological treatments, including established antiviral

drugs licensed in treating other infections, have been used and promoted as potential treatments for Covid-19 (Sanders et al., 2020). However, at the time of writing, no pharmacological treatments have been proven reliable to be used as a safe and effective therapy (De Crescenzo et al., 2021). Research suggests that supportive care has been adopted as the mainstay of management (De Crescenzo et al., 2021), focusing on rehabilitative treatments to assist those who have experienced impairment from Covid-19 (De Crescenzo et al., 2021). Rehabilitative measures seek to maximise individuals' functional ability to return to activities of daily living (De Biase et al., 2020). To the best of our knowledge, whether treatments influence the relationship between Covid-19 and cognitive function has not been investigated. Therefore, we did not make specific predictions about how treatments impact cognition.

CHAPTER 2: METHODS

We designed, pre-registered, and reported the meta-analysis results per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Moher et al., 2015). Figure 1 depicts the major steps of the meta-analysis; any deviations from the preregistration are denoted in text.

Open Science Disclosure

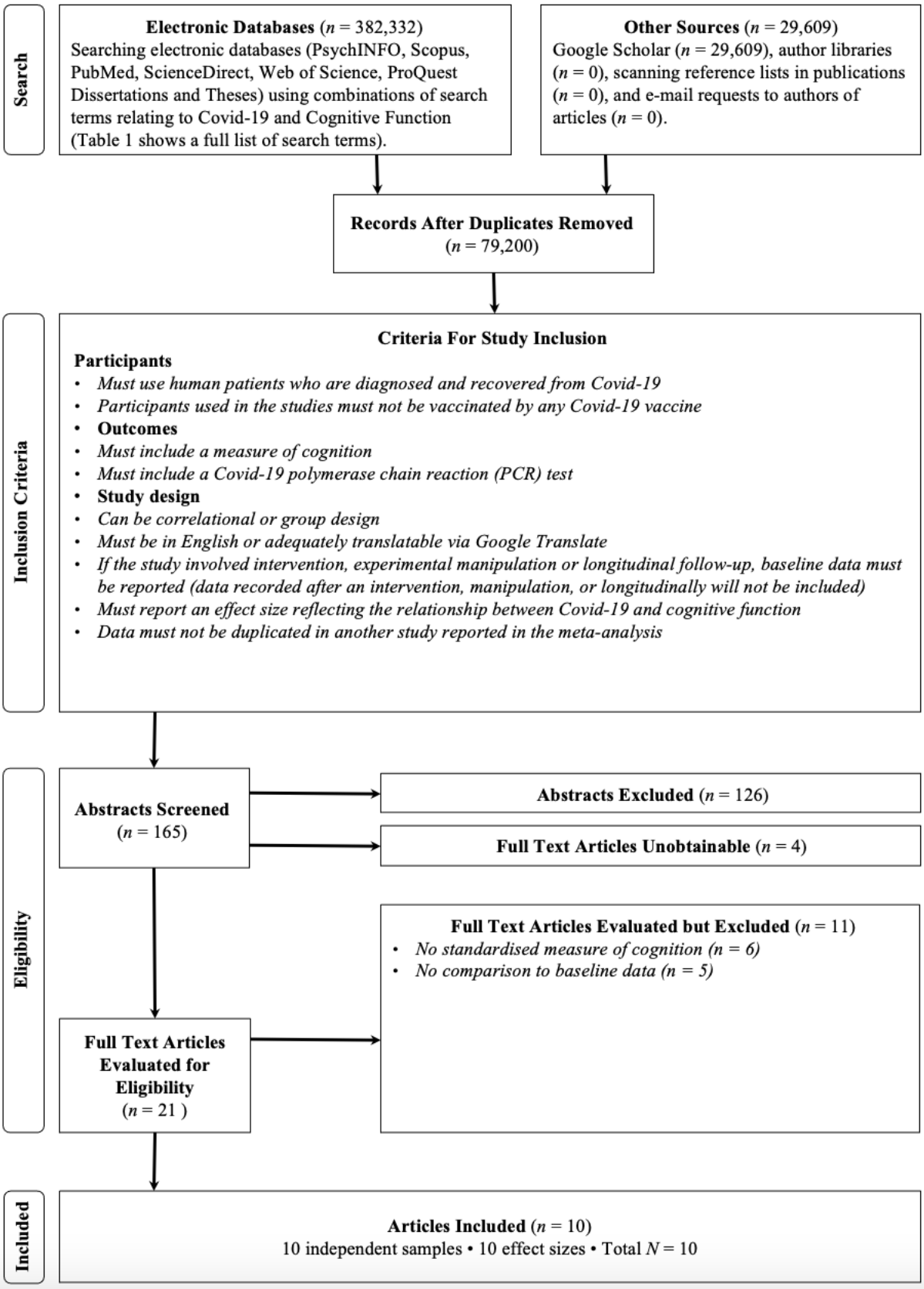
We shared all procedures, materials, datasets, and code on the Open Science Framework https://osf.io/kbuxn/?view_only=f976139a7021473fb525f71c70a27992 and provided this information in the Supplemental Material. Systematic data collection commenced on 10 August 2021. There are no other unreported/unlinked preregistrations for this meta-analysis project.

Inclusion and Exclusion Criteria

Since our meta-analysis aimed to determine whether recovered Covid-19 patients had cognitive deficits, we established strict inclusion and exclusion criteria. First, the studies had to include adequate statistical information for computing the effect size for Covid-19 on cognitive function in recovered patients. In cases of missing statistical data, we first attempted to contact the authors (Polanin et al., 2020). If we could not obtain the required statistics, we excluded the articles, even if the articles met all other search criteria. Second, we excluded articles not written in English unless we obtained all necessary data and information for coding in English or obtained such data and information from the authors. Third, we included both published or unpublished studies from 1 January 2020 to 31 August 2021. Four, we excluded retracted studies if the retraction is due to data collection and analysis problems (Fanelli et al., 2021).

Figure 1

Search Flow Diagram



Note. This figure has been reproduced and edited with permission from "Template2_SearchFlowDiagram.pptx" in Moreau, D., & Gamble, B. (2020). Conducting a meta-analysis in the age of open science: Tools, tips, and practical recommendations. Psychological Methods. https://doi.org/10.1037/met0000351

Literature Search and Coding

To find articles relevant to our topic, we used Google Scholar, PsychINFO, Scopus, PubMed, Science Direct, ProQuest Dissertations & Theses Global, and Web of Science and identified a sample of studies based on various steps illustrated in Figure 1. In the first initial online search, we decided to identify articles including variations of keywords such as Covid-19 and cognition, aimed to identify relevant literature, related topics and the scholars in this field. As a result of the first search round, we were able to identify more specific search terms on Covid-19 and cognition. Boolean Logic operators such as "OR" and "AND" were used in the search pattern to connect Covid-19 and cognition. A list of search terms is listed in Table 1 in the appendices. Search syntax, date of searches, and the number of results returned for each database used in the meta-analysis are listed in Table 2. All database searches achieved 382,332 hits. The date last searched was 31 August 2021. Endnote and Rayyan removed any duplicates and selected eligible studies from the database findings. After adjusting for duplicates, a total of 79,200 published articles, unpublished articles, and datasets were initially identified and downloaded from the primary database search. It should be noted that often duplicates were removed manually due to the inability of Endnote or Rayyan to identify as such; therefore, the total number of articles in the dataset is approximate.

We first included studies that required contacting the author for the dataset/further clarifications into the main coding sheet, but we documented them as to be excluded potentially, should the author not respond by a given date. We contacted authors of studies with missing necessary statistics for relevant datasets/information. If the original authors of studies provided the dataset, the researchers conducted needed analyses for coding. We documented this process and the relevant results in *DataExtracted_Yes_No_Mods.csv* within the coding sheet under the notes tab. We saved all final studies included in the total search into a cloud folder, accessible

from https://osf.io/kbuxn/?view_only=f976139a7021473fb525f71c70a27992 or directly within the Supplemental Materials. In total, we contacted 24 authors, four responded with additional data that were eventually included in our meta-analysis (Appelbaum et al., 2018). After the above search procedures, M. Mudgway scanned all abstracts, tables and method sections to identify the relevance of the sources. If the articles indicated relevance for our analysis, M. Mudgway read more of the articles to determine whether they met the inclusion criteria or whether articles had to be excluded based on our search criteria (see next paragraph). A second scan round enabled us to exclude 79,178 articles not meeting our search criteria, reducing our sample of studies to 10 studies with a total of 1065 participants. We listed all the included studies in Table 3.

Table 2

Search Syntax, Date of Searches, and Number of Results Returned for Each Database Used in Meta-Analysis

Database	Date of Coverage	# Results	Search Syntax	Notes
PsychINFO	[10 August 2021 - 31 August 2021]	[4,437]	[(Covid-19 and Cognitive).ab.ti]	Date limit imposed (2020-2021); periods not valid in search, space used to ensure numerical values were identified in text.
Scopus	[10 August 2021 - 31 August 2021]	[237,023]	[TITLE-ABS(*Covid-19 AND *Cognitive)]	Limited to journal article; date limit imposed (2020-2021).
ProQuest Dissertations & Theses Global	[10 August 2021 - 31 August 2021]	[148]	[ab(Covid-19) AND ab(Cognitive)]	Date limit imposed (2020-2021).
Web of Science	[10 August 2021 - 31 August 2021]	[35,724]	[TI=(Covid-19* AND Cognitive) AND AB=(Covid-19* AND Cognitive)]	Limited to journal articles; date limit imposed (2020-2021); only abstract searched.
Google Scholar	[10 August 2021 - 31 August 2021]	[29,609]	[“Covid-19” and “Cognitive’]	Date limit imposed (2020-2021); results extracted up to 500.
Science Direct	[10 August 2021 - 31 August 2021]	[6,265]	[Abstract - Covid-19 AND Cognitive / Title - Covid-19]	Date limit imposed (2020-2021); wildcards not valid within database.
PubMed	[10 August 2021 - 31 August 2021]	[69,126]	[Covid-19[Title/Abstract] AND Cognitive[Title/Abstract]]	Date limit imposed (2020-2021).

Screening

Studies collected through the database searches and contacting authors were assessed for their eligibility based on their titles, abstracts and contents. We sought additional information from study authors where necessary to resolve questions about eligibility or where data were insufficient to calculate an effect size. The full-text articles for each study deemed eligible by M. Mudgway (n = 10) were further reviewed by D. Moreau for confirmation of inclusion and reliability purposes. We documented and explained all decisions for inclusion and exclusion clearly, transparently and systematically in articles.csv, which is accessible in the provided Supplemental Materials. We provided the details of articles/studies excluded at the screening stage and eligibility stage in Figure 1. We scanned all articles to determine whether we should include them in the main coding sheet or not.

Table 3

Studies Included in the Meta-Analysis

Study	N	Region	Design	Published
Frontera et al. (2021)	382	North America	Prospective cohort	Yes
Miskowiak et al. (2021)	129	Europe	Prospective cohort	Yes
Raman et al. (2020)	88	Europe	Prospective cohort	Yes
Woo et al. (2020)	28	Europe	Cross-sectional	Yes
Blazhenets et al. (2021)	8	Europe	Prospective cohort	Yes
Del Brutto et al. (2020)	93	South America	Longitudinal prospective cohort	Yes
Pirker-Kees et al. (2021)	14	Europe	Experimental	Yes
Triana et al. (2020)	142	NA	Retrospective cohort	Yes
Delgado-Alonso et al. (2021)	50	NA	Cross-sectional	No
Serrano-Castro et al. (2021)	131	Europe	Cross-sectional	No

Coding

We used Rayyan to develop a data coding sheet to keep a clear record of our decisions at different stages and enhance reproducibility (Arslan, 2019; Obels et al., 2020; Siddaway et al., 2019). We documented gaps and reported decisions in detail in *articles.csv***.** M. Mudgway coded the studies, D. Moreau verified, and M. Mudgway adjusted where necessary.

Included Studies Coding

Once we completed and confirmed the included studies, M. Mudgway coded the studies independently. We coded included study information transparently, including authors' names, year, study number, sample description, demographics, publication status, inferential statistics, variables information, effect size calculation method, moderator category, moderator explanation, with descriptions/explanations and quotations, including page and table numbers, from the included studies. This can minimise possible errors, maximise reproducibility, and facilitate verification by peer-reviewers or other researchers. Please refer to *DataExtracted_Yes_No_Mods.csv* and *ExtractedArticles.csv* in the Supplemental Material for the complete coding sheet. Moreover, we verified inferential statistics and effect sizes in primary studies and our calculation, using metafor, an R package developed by (Viechtbauer, 2010).

Variables and Design in the Studies

The included studies included both continuous and categorical variables. These variables were categorised in moderator categories to be accurately measured. The variables and designs of the studies are listed in Table 4 in the appendices.

Meta-analytic Procedure

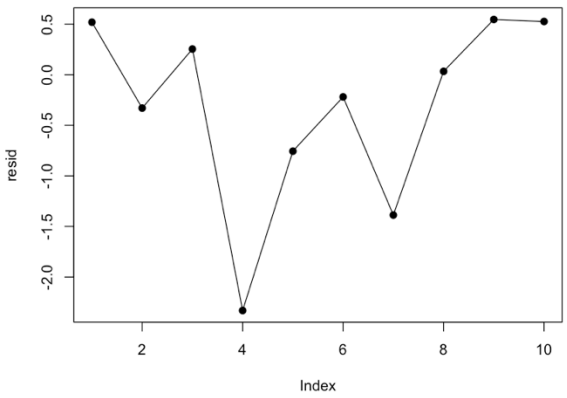
We used random-effects meta-analysis modelling with restricted maximum likelihood to estimate overall effects and the heterogeneity across included studies. We also used mixed-effects meta-analysis modelling to test whether the moderator variables could explain differences in the strength of effect sizes across studies. Analyses were run in the R software environment (Version 3.6.0; R Core Team, 2019) using the metafor package (Viechtbauer, 2010); our R script is available

online https://osf.io/kbuxn/?view_only=f976139a7021473fb525f71c70a27992 and in the Supplemental Materials. We converted all effect sizes into Hedge's *g* to facilitate comparison and calculated 95% confidence intervals (CIs) for the overall effect size and inferred confidence in the cumulative estimate from a combination of the magnitude and precision of the effect size and risks of publication and reporting bias. For missing data (e.g. effect size missing, but M and SD reported), we calculated using R package esc (Lüdecke et al., 2019). *Meta-analysis_Main.R* in the Supplemental Materials documented Calculation or coding procedures. Whenever available, we collected standardised effect sizes directly from authors of original papers. We checked for the accuracy of these analyses based on provided information and details. We used descriptive statistics such as mean and standard deviation to re-compute standardised effect sizes. We documented all conversions and coding decisions. To facilitate reproducibility, we included the original quotes and table/page numbers from the original articles into the coding sheet.

Biases were assessed using a combination of p-curve analysis, published versus unpublished study comparisons, and examination of study quality. M. Mudgway assessed study quality using the Checklist for Measuring Quality by Downs and Black (1998) and adapted the checklist to suit the current meta-analysis. Outliers were predefined as correlations whose residuals had *z* scores > 3. No studies met this threshold, as illustrated in Figure 2, and so none were excluded from the primary analyses. Noting that one effect size deviated from the mean (see Figure 2), we also explored an alternate measure of outliers, Cook's distance (D_i), which indicates the relative influence of each effect size on the summary estimate. A standard rule of thumb is that D_i values greater than three times the mean D_i may be potential outliers. No effect sizes exceeded this threshold, as illustrated in Figure 3. Small differences occurred in the summary estimate and results of the moderator

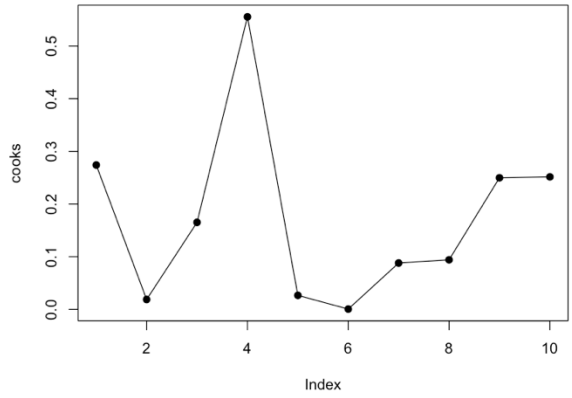
analyses. These secondary analyses are available in the attached Supplementary Material folder, but we focus here on the initial analyses run with all effect sizes.

Figure 2
Standardised Residuals



Note. Standardised residuals of each effect size (k= 10) included in the main random effects model. Outliers were pre-defined as effect sizes with standardised residuals greater than 3; none met this threshold and so none were excluded from the primary analyses.

Figure 3
Cook's Distance (D_i)



Note. Cook's distance (D_i) scores for each effect size included in the main random effects model (k = 10).

CHAPTER 3: RESULTS

The studies encompassed a range of participants, from hospitalised to non-hospitalised, and a multiplicity of cognitive function tasks across the ten included articles. Researchers used four different measures to capture some aspects of impairment in cognition, including; Montreal Cognition Assessment, Cognitive Impairment in Psychiatry, Telephone Instrument for Cognitive Status, and Cognitrone. Figure 4 shows that all (10 of 10) group differences between Covid-19 and cognitive function were negative; that is, cognition was impaired for individuals who had recovered from Covid-19. The meta-analytic effect was g = -.53, 95% CI [-0.75, -0.31], p = 0.0000019, k = 10. There was a moderate degree of heterogeneity across effect sizes, as might be expected from the diversity of cognitive function tasks.

The I^2 statistic indicates the percentage of between-studies variability in effect sizes due to heterogeneity rather than random error, was I^2 = 57.69% for the overall model. We also used Tau-squared to analyse the heterogeneity further to determine the variance of the effect size parameters across the population of studies and the variance of the true effect sizes. τ^2= 0.0633 (SE = 0.0552), and tau (square root of estimated tau^2 value) = 0.2516. In the analyses reported next, we investigated whether some of the heterogeneity across studies could be explained by the moderator variables. Summarised results of the meta-analysis are provided in Table 5.

Cognitive Domains

We examined three cognitive domains: attention, executive function and memory. We used a random-effects meta-analysis model to test if there was a meaningful moderating effect. The effect of cognitive domains was significant QM(df = 3) = 10.5445, p = 0.0145. Attention was negative and significant, g = -.8893, 95% CI = [-1.4877, -0.2909], p = 0.0036, k = 11. Executive function was negative and significant g = -.8906, 95% CI = [-1.4528,

-0.2783], p = 0.0039, *k* = 11. Lastly, memory was negative and significant *g* = -.8906, 95% CI = [-1.4756, -0.3057], *p* = 0.0028, *k* = 11. We did not make specific predictions regarding cognitive domains. These results suggest multiple cognitive domains are at risk from Covid-19, however it is important to note that the small sample size in the cognitive domain analysis indicate that results should be interpreted cautiously.

Figure 4

Forest Plot of Random Effects Model Effect Sizes

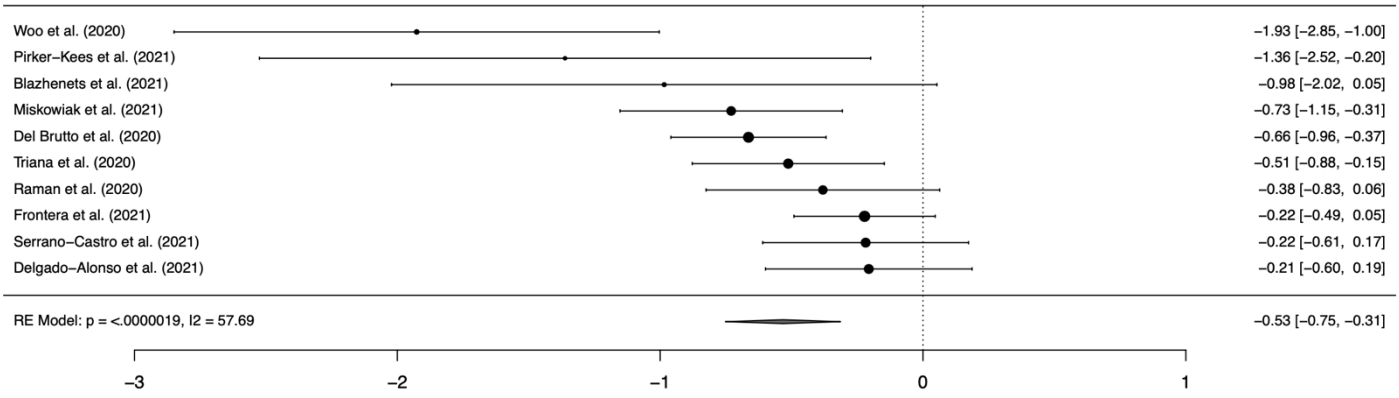


Table 5

Summarised Results of the Meta-Analysis

Hypotheses	Key findings / theories in the literature	Findings in the meta-analysis
Covid-19 impacts cognitive function in patients who have recovered		
The evidence is in support of Covid-19's impact on cognitive function being meaningfully different from the null.	The meta-analytic effect was negative and significant.	Supported.
Theoretical Moderator Hypotheses		
Age: cognitive impairment is stronger under older age groups.	There is no support that age has a moderating effect on cognitive impairment. Limited data indicates these results may change with future research.	Not supported.
Race/ethnicity: cognitive impairment differs depending on race/ethnicity.	There is no support to suggest that race/ethnicity has a moderating effect on cognitive impairment.	Not supported.
Sex: no prediction.	We cannot make specific conclusions on male and female outcomes due to mixed-results and mixed-research. These results may change with future research.	Females; non significant effect. Male; non significant effect.
Regional differences: no prediction.	All moderator subgroups contained small effect sizes, possibly hampering our ability to detect a true difference. Further research is needed to determine whether regional differences have a true effect.	Europe; negative and significant. North America; negative and not significant. South America; negative and not significant.
Disease severity: no prediction.	Mild Covid-19 was significant, suggesting severity of Covid-19 may predict outcomes for cognitive impairment.	Mild severity; negative and significant. Severe severity; negative and not significant.
Strain variants: no prediction.	Not reported in studies.	Nil.
Genetic variants: no prediction.	Not reported in studies.	Nil.
Treatments: no prediction.	There is no evidence to suggest that treatment for Covid-19 will be a predictor of cognitive impairment.	With treatment; negative and significant. Without treatment; negative and significant.
Additional Exploratory Analysis		
Comorbidities: no prediction.	Mental comorbidities had a stronger effect, indicating patients with Covid-19 are at higher risk of cognitive dysfunction if a mental comorbidity is present.	Mental comorbidities; negative and significant. Physical comorbidities; negative and not significant.

Moderator Analyses

We examined eight possible theoretical and methodological moderators according to a pre-registered criteria and coding sheet: race/ethnicity, age, sex, regional differences, disease

severity, strain variants, genetic variants, and treatments. Results of moderator analysis are summarised in Table 6.

Moderator Analyses of Participant Characteristics

We used a random-effects meta-analysis model to test if there was a meaningful moderating effect. We analysed the effect of three racial-ethnic groups, Black peoples, White peoples and 'other', classified as minority racial-ethnic groups mentioned within the included studies, including Asian, Hispanic, and Latino. The effect of White racial-ethnic groups was not significant QM(df = 1) = 0.0003, p = 0.9866, g = .0001, 95% CI = [-0.0085, -0.0086], p = 0.9866, k = 2. The effect of Black racial-ethnic groups could not be analysed due to only one study reporting data. Lastly, the effect between 'other' racial-ethnic groups was not significant QM(df = 1) = 0.0003, p = 0.9866, g = -.0004, 95% CI = [-0.0494, 0.0485], p = 0.9866, k = 2. Contrary to our prediction, we found no support for a moderation effect of racial-ethnic groups.

The effect of age was not significant, QM(df = 1) = 0.4015, p = 0.5263. Age had an effect of g = .0105, 95% CI [-0.0220, 0.0430] p = 0.5263, k = 8. Contrary to our prediction, we found no support for a moderation effect of age. The effect of female sex was not significant, QM(df = 1) = 0.0250, p = 0.8744. Female sex had an effect of g = .0017, 95% CI = [-0.0189, 0.0223], p = 0.8744, k = 9. The effect of male sex was not significant, QM(df = 1) = 0.0150, p = 0.9024. Male sex had an effect of g = -.0017, 95% CI = [-0.0223, 0.0189], p = 0.8742, k = 9. We did not make specific predictions on the impact of Covid-19 and cognition on sex differences due to the mixed results in current research. These results suggest we may not be able to predict Covid-19 outcomes based on sex differences.

The effect of regional differences was significant QM(df = 3) = 12.1743, p = 0.0068. The effect between Covid-19 and cognitive function was negative and non significant for

North America and South America. North America had an effect of g = -.2223, 95% CI [-1.2247, 0.7801], p = 0.6638, k = 9. South America had an effect of g = -.6639, 95% CI [-1.6737, 0.3459] p = 0.1975, k = 9. Europe had a negative and significant effect of g = -.7998, 95% CI [-1.2877, -0.3119], p = 0.0013, k = 9.We did not make specific predictions as to how regional differences would impact cognition.

Moderator Analyses of Clinical Characteristics

We used a random-effects meta-analysis model to test if there was a meaningful moderating effect. The effect of disease severity was significant QM(df = 2) = 12.2172, p = 0.0022. Mild severity had an effect of g = -.8545, 95% CI [-1.4301, 0.2788], p = 0.0036, k = 7. Severe severity had an effect of g = -.6496, 95% CI [-1.3068, 0.0076], p = 0.0527, k = 7. Mild Covid-19 was significant, suggesting those with mild cases of Covid-19 may be at risk of cognitive impairment. Treatment was significant QM(df = 2) = 23.3673, p = < .0001. Patients who received pharmaceutical or medical device treatment had an effect of g = -.4363, 95% CI [-0.7709, -0.1016], p = 0.0106, k = 10. Patients who did not receive pharmaceutical or medical device treatment had an effect of g = -.6038, 95% [-0.8921, -0.3154], p = <.0001, k = 10. We found no support to suggest patients who received treatment would have better cognitive outcomes after recovering from Covid-19. We pre-registered to analyse Covid-19 strain variants and genetic variants which may predispose individuals to illness; however, we did not find any information regarding these moderating effects in any reported studies.

Additional Exploratory Analyses

In addition to planned, pre-registered analyses, we also explored the effects of one moderator variable not identified in the preregistration: comorbidities. We made no

prediction about the moderating influence of comorbidities but were motivated to explore its effects given the frequency comorbidities were reported in the documented studies. The effect of comorbidities was significant QM(df = 2) = 7.3802, $p = 0.0250$. Mental comorbidities had a negative significant effect of $g = -.5745$, 95% CI [-1.0337, -0.1153], $p = 0.0142$, $k = 7$. Physical comorbidities had a negative effect but was not significant of $g = -.4778$, 95% CI [-1.2788, 0.3232] $p = 0.2423$, $k = 7$. Mental comorbidities effect was stronger, indicating patients with Covid-19 might be at a higher risk of cognitive dysfunction if a mental comorbidity is present. We found no support for a moderation effect of physical comorbidities. Summarised results of the moderator analysis are provided in Table 6.

Table 6

Summarised Results of the Moderator Analysis

Moderator	k	QM(df)	Effect Size*	95% CI	*p*-value
Race/ethnicity					
White	2	QM(df = 1) = 0.0003	.0001	[-0.0085, -0.0086]	0.9866
Black	0	Nil	Nil	Nil	Nil
Other	2	QM(df = 1) = 0.0003	-.0004	[-0.0494, 0.0485]	0.9866
Age	9	QM(df = 1) = 0.4015	.0105	[-0.0220, 0.0430]	0.5263
Sex - Female	9	QM(df = 1) = 0.0250	.0017	[-0.0189, 0.0223]	0.8744
Sex - Male	9	QM(df = 1) = 0.0250	-.0017	[-0.0223, 0.0189]	0.8742
Regional Differences	9	QM(df = 3) = 12.1743	North America; -.2223. South America; -.6638. Europe; -.7998.	North America; [-1.2247, 0.7801]. South America;[-1.6737, 0.3459]. Europe;[-1.2877, -0.3119].	North America; 0.6638. South America; 0.1975. Europe; 0.0013.
Disease Severity	7	QM(df = 2) = 12.2172	Mild; -.8545. Severe; -.6496.	Mild; [-1.4301, 0.2788]. Severe; [-1.3068, 0.0076].	Mild; 0.0036. Severe; 0.0527.
Treatment	10	QM(df = 2) = 23.3673	With; -.4363. Without; -.6038	With; [-0.7709, -0.1016]. Without; [-0.8921, -0.3154].	With; 0.0106. Without; <.0001.
Genetic variants	Nil	Nil	Nil	Nil	Nil
Strain variants	Nil	Nil	Nil	Nil	Nil
Additional Exploratory Analysis					
Comorbidities	7	QM(df = 2) = 7.3802	Mental; -.5745. Physical; -.4778.	Mental; [-1.0337, -0.1153]. Physical; [-1.2788, 0.3232].	Mental; 0.0142. Physical; 0.2423.

Note. k = number of samples; N = total number of individuals in k; [Abbreviation of effect size unit = Long form of effect size, e.g. g = Hedge's g effect size], CI = lower and upper limits of 95% confidence interval, * $p < .05$, ** $p < .01$, *** $p < .001$, (all two-tailed**).**

Assessment of Bias

We used several techniques to examine publication and reporting biases across the included studies. First, we examined whether the meta-analysis showed evidence of "small-study effects" wherein smaller studies often show different, stronger effects than larger studies, possibly reflecting publication bias (Schwarzer et al., 2015). To this end, we inspected a funnel plot of the relationship between effect size and standard error (Figure 5). Suppose a meta-analysis is free from small-study effects. In that case, effect sizes derived from larger samples (and thus with smaller standard errors) are expected to cluster around the mean, whereas effect sizes derived from smaller samples (and thus with larger standard errors) should be broadly dispersed and distributed symmetrically around the mean, forming a funnel-like shape (Gamble et al., 2019).

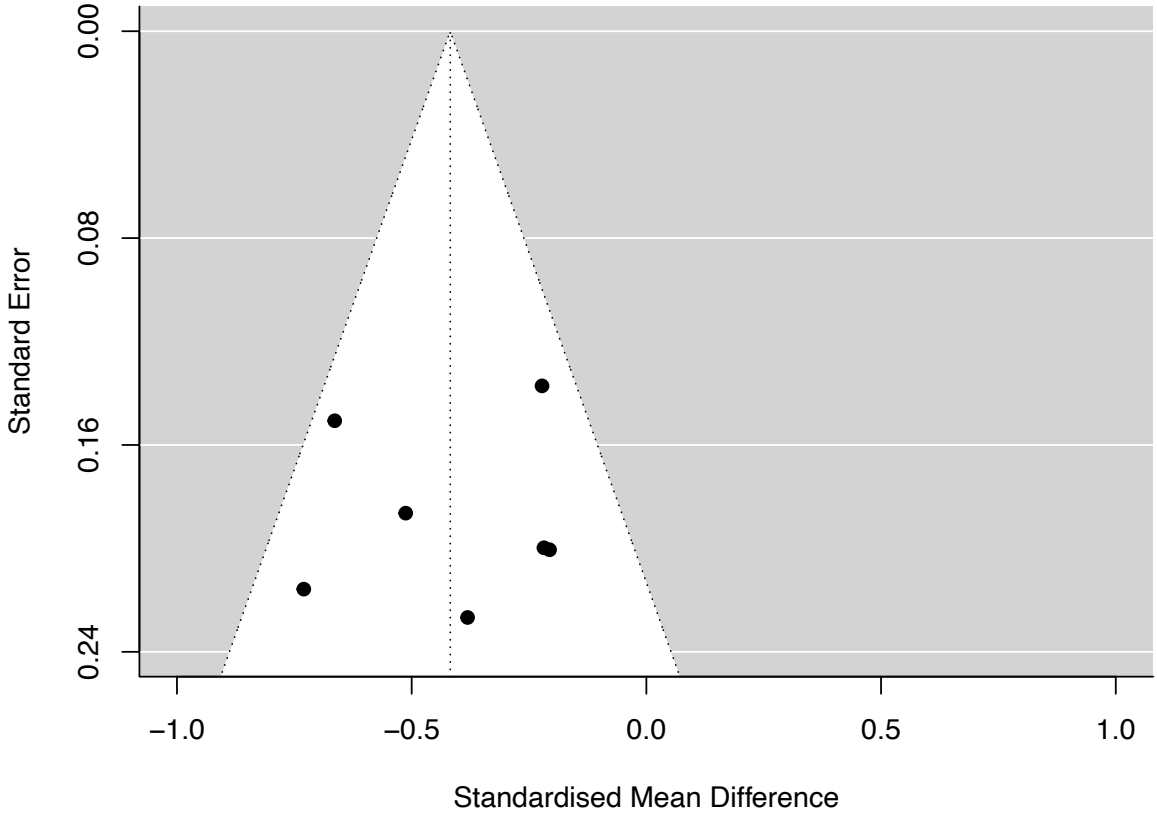
The funnel plot for this meta-analysis shows scattered studies to either side of the overall effect line in a symmetrical manner, suggesting no known biases in our research. Current research indicates that funnel plots of the standardised mean difference plotted against the standard error are susceptible to distortion, leading to overestimating the existence and extent of publication bias (Zwetsloot et al., 2017). With this being said, in the absence of large a sample size and extensive, thorough research on Covid-19 and its association with cognitive function, we suggest the findings of this research are interpreted with caution. Second, to test for inflation of the effect in the published literature relative to the true effect, we compared the magnitude of effect sizes in published versus unpublished studies. A moderator analysis showed that the effect of publication status was not significant QM(df = 1) = 2.7915, p = 0.0948, indicating there are no differences in Covid-19's impact on cognitive function in either published (g = -.4109, 95% CI = [-0.8930, 0.0711], p = 0.0948, k = 10) or unpublished studies. However, it should be noted that only two independent studies contributed to the unpublished subgroup of effect sizes. Third, we

assessed whether the quality of studies influenced the strength of the effect. The moderating effect of quality was not significant, QM(df = 1) = 0.2216, g = .1455, 95% CI [-0.4604, 0.7514], p = 0.6379, k = 10, suggesting the included effect sizes were not biased by differences in methodological quality. Quality ratings for each study are presented in Table 7 in the Appendices.

Looking across included studies marked strengths and weaknesses. For example, all studies clearly described hypothesis (100%), main findings (100%), participant characteristics (100%), and withdrawals and dropouts (90%), but few reported power analyses (20%). Finally, we ran a *p*-curve analysis (Simonsohn et al., 2014) to assess whether the *p*-value distribution for statistically significant ($p < .05$) effect sizes in the meta-analysis aligned with the *p*-value distribution expected from a true effect. A *p*-curve for a true effect should be right-skewed; it should contain more low (0.1) than high (0.4) significant *p*-values (Simonsohn et al., 2014). The *p*-curve for this meta-analysis (generated via the app at p-curve.com) was heavily right-skewed, indicating no evidence of publication bias or selective reporting of significant results in the included studies, as depicted in Figure 5. The *p*-curve analysis also provided an estimate of the statistical power of studies that yielded significant *p*-values; for this meta-analysis, power was estimated to be 99%, 90% CI = [99%, 99%], indicating that these studies, on average, were well powered to detect true effects. We also calculated statistical power for all studies based on effect size, average sample size, number of effect size, and heterogeneity to get a power calculation of 0.99, further demonstrating that these studies, on average, were well powered to detect true effect sizes.

Figure 5

Funnel Plot of the Relationship Between Effect Size and Standard Error



CHAPTER 5: DISCUSSION

Cognitive dysfunction is consistently observed in viral outcomes (Matos et al., 2021; Ritchie et al., 2020; Tarter et al., 2014), but whether Covid-19 contributes to cognitive impairment has not, until now, been the focus of a comprehensive meta-analysis. By examining the currently available evidence from a range of sources, including seven electronic databases, this meta-analysis provides the most complete account to date of the links between Covid-19 and its impact on the cognitive function of recovered patients. We found that Covid-19 had a moderate effect (g = -.53) on cognitive function in individuals who had recovered from Covid-19. These results are likened to reports of Long Covid cognitive symptoms that persist beyond the acute and sub-acute phases post Covid-19 infection (Hampshire et al., 2021). Long Covid refers to complaints of "brain fog", low energy, problems concentrating, disorientation and other psychological symptoms persisting after recovery from Covid-19 (Hampshire et al., 2021). Research examining Long Covid is gradually developing, proving that Covid-19 patients can develop various neurological symptoms, including encephalopathies, inflammatory syndrome, autoimmune responses, microbleeds and stroke (Hampshire et al., 2021). Further research on neurological consequences and Long Covid revealed that individuals might experience elevated cerebrospinal fluid antibodies, white matter change in the brain, and psychiatric and psychological consequences at the point of discharge (Kumar et al., 2021). However, much of the research is based on self-reported cognitive problems and small-scale studies, with little information on whether Covid-19 infection is associated with objectively measured cognitive impairment or how this differs with population-level hospitalisation status and respiratory symptom severity (Hampshire et al., 2021). Although limited data is associated with Covid-19 and cognitive deficits at a population level, cognitive problems are becoming increasingly evident. Nonetheless, measuring the magnitude of these cognitive deficits is challenging.

Covid-19 is unpredictable with ongoing mutations, limiting longitudinal cognitive data pre and post-infection (Hampshire et al., 2021). The lack of longitudinal data is exacerbated by the expense of undertaking cognitive assessments against large populations to record changes and control confounding variables associated with cognitive performance (Hampshire et al., 2021). Previous studies have been limited in their scope as they lack sufficient evidence to account for key sociodemographic variables associated with Covid-19, such as age, racial-ethnic groups and pre-existing medical conditions (Hampshire et al., 2021). Although data may be limited, we attempted to examine the available research to give the most thoughtful account to date of Covid-19's impact on cognitive function. We used a random-effects model to address our study's moderate heterogeneity. Random-effects models are effective as they assume that the true effect is not the same in all studies and that the studies were drawn from different populations (Bell et al., 2019). To further examine the cause of the moderate heterogeneity, we ran moderator analysis on several variables related to differences in samples and study designs. Although some of the moderating variables displayed nonsignificant results, we identified four that significantly affected the strength of the relationship between Covid-19 and cognitive function: regional differences, treatment, comorbidities, and illness severity. We discuss each significant moderator in turn before addressing the nonsignificant moderator variables.

Significant Moderators

Cognitive function was indeed more reduced in comorbidities. The coexistence of comorbidities with Covid-19 has consistently been reported as a risk factor for unfavourable prognosis. The differences in the effect across comorbidities were not unexpected; for physical comorbidities, the effect was negative and nonsignificant, and for mental comorbidities, the effect was negative and significant. These findings align with current

research on physical comorbidities (Gordon et al., 2021; Wang et al., 2020) and findings on mental comorbidities and virus outcomes (Liu et al., 2021; Severance et al., 2011; Stein, 2021). When looking at physical comorbidities, patients with obesity, hypertension, cerebrovascular disease or pulmonary dysfunction are most likely to develop symptoms that predispose individuals to cognitive decline (Gordon et al., 2021). Research suggests these individuals often become severely ill with Covid-19 and die from their original comorbidity (Wang et al., 2020). Therefore, it would be beneficial to accurately evaluate all original comorbidities of individuals with Covid-19 to accurately picture the underlying mechanisms associated with physical comorbidities and cognitive dysfunction. It is suggested that animal models mimicking human comorbidities could be an effective strategy to help understand the contribution of other diseases in the progression associated with cognitive deficits (Gordon et al., 2021). Concerning mental comorbidities, research has shown a bidirectional relationship between mental health and Covid-19 (Taquet et al., 2020). It suggests that individuals with cognitive disorders have a higher risk for Covid-19, with the virus accelerating the probability of mental illness, cognitive impairment, the risk for dementia and brain ageing (Meier et al., 2021). A biological assumption for this association is how SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells (Abboud et al., 2020; Baig et al., 2020; Lu et al., 2020). These receptors are expressed in neurons in the brain and glial cells, causing damage and changes to the nervous system and impairing synapse function (Abboud et al., 2020; Baig et al., 2020; Lu et al., 2020). Social distancing and isolation in an attempt to avoid contamination of Covid-19 contribute to the risk of mental comorbidities, including depression and other mental disorders, therefore contributing to the increased risk of cognitive decline and increasing the risk of neurodegenerative disorders, such as Alzheimer's disease (Fontes et al., 2020). The risk of Alzheimer's disease is perpetuated through the biological mechanisms linking mental disorders through

hypothalamic-pituitary–adrenalin axis dysregulation, hippocampal atrophy, inflammatory changes, and increased amyloid deposition (Dafsari and Jessen, 2020). Current research suggests that compliance with health practices and social distancing depends on an individual's working memory, highlighting a complex relationship between SARS-CoV-2 infection and cognitive function (Xie et al., 2020). Whatever the underlying mechanism, these findings have important clinical implications. It follows that predictions can be made on outcomes of these individuals in a hospital setting and can assist with recommendations for practical cognitive tasks, for example, cognitive rehabilitation therapy and cognitive-motor training.

Cognitive rehabilitation therapy (CRT) attempts to enhance independence and functioning using various interventions and aims to improve brain function or lessen the disabling impact of cognitive impairment (Sale & Gentile, 2018; Zarrabian & Hassani-Abharian, 2020). Research suggests CRT is an effective way to increase an individual's capacity for information processing and can be effectively used on individuals at risk of cognitive decline from Covid-19 (Zarrabian & Hassani-Abharian, 2020). Cognitive-motor training is an effective method used commonly with elderly patients, which encourages balance training alongside a simultaneous motor task to encourage cognitive and motor systems (Amini et al., 2022). This training has led to consistent positive results and may assist in Covid-19 cognitive recovery. Recent studies have also reported the benefits of using computer-based cognitive games and brain exercises to improve cognition (Bozoki et al., 2013). Cognitive rehabilitation is advantageous to enhance the cognition of the diverse Covid-19 population.

Our next significant moderator identified that those in Europe exhibited a more substantial reduction in cognitive function than those in North America and South America. These results quantify Covid-19's effect on the economy, health, quality of life and

government handling of the pandemic. There are various reasons why Covid-19 and cognitive impairment may be significant in some regions but not others; one reason may relate to political views associated with lockdowns and vaccination mandates. As the vaccination process began, the pandemic continued to rage in many countries worldwide. It is assumed the pandemic continued largely because the proportion of the population vaccinated against the virus in these countries was insufficient to reach herd immunity (Albrecht, 2022). Significant factors in inadequate vaccine uptake are the insufficient capacity to reach populations, vaccine hesitancy and overall resistance to government mandates (Albrecht, 2022). Understanding why people are refusing to be vaccinated and the role of political views in these decisions is a question of utmost significance since these choices have severely hampered efforts to control Covid-19. The role of politics has had a critical impact on Covid-19 responses to the pandemic and are expected to drive both direct and indirect impacts on Covid-19 cases and deaths (Albrecht, 2022).

Different regional incidence rates may vary depending on the exposure of groups and backgrounds of individuals, with outbreaks varying regarding incidence between geographical regions (Moshammer et al., 2022). One aspect relative to geographical regions is associated with population density. Population density has been used as a surrogate measure of social distancing capacity, and studies have shown that Covid-19 transmission is potentially more likely to occur among cities with higher population densities (Moshammer et al., 2022). Considering that only population density can provide high explanatory power in the variation of cumulative cases for Covid-19, it is likely that population density can also be a competent explanatory variable for airborne infectious diseases (Wong & Li, 2020). Current research on regions assumes that socioeconomic factors, particularly education level, may be necessary for disease prevention and mortality (Abedi et al., 2021). Research in Austria showed that sociodemographic differences and low-income influence cases and

deaths (Moshammer et al., 2022). Aside from sociodemographic and socioeconomic factors, specific geographical factors such as sea level may play a part in case rate and severity. For individuals who live in environments of high altitudes of more than 2500m above sea level, altitude seemed to play a protective factor against case severity (Arias-Reyes et al., 2020). Additionally, a Peruvian study indicated that with every 500m of altitude, Covid-19 cases reduced by 22% and the death rate by 40% (Accinelli & Leon-Abarca, 2020). Research has also indicated that air quality is significantly associated with Covid-19 death rates (Moshammer et al., 2022). Poorer air quality is also associated with more severe cases of Covid-19 and higher infection rates (Moshammer et al., 2022). Nonetheless, there is limited data on how Covid-19 affects individuals' cognition from different regional locations. Because of the limited data surrounding regions in our research, we cannot make exact conclusions as to why Europe is more affected by cognitive impairments than other regions. Therefore, examining regional differences and the impact of Covid-19 on cognition is warranted considering the array of research that can be produced when more data is available.

The next moderator that was significant was disease severity. We predicted that disease severity does not indicate cognitive deficits; however, our results present that mild severity was significant, suggesting severity is associated with cognitive outcomes. Post-acute cognitive impairment is becoming more prevalent among individuals with mild Covid-19, as evident in our results. What is most evident for mild Covid-19 cases is the experience of fatigue, lack of concentration, and difficulty in focusing, all symptoms that have been associated with and related to mild cognitive impairments and are conceptually defined as "brain fog" (Graham et al., 2021; Hampshire et al., 2021). Although there is limited research available to understand the effects of Covid-19 severity on cognitive function, current research suggests that cognitive impairment is as high as 81% in severe cases requiring hospitalisation (Henneghan et al., 2022). Contrary to this research, our results showed that

severe Covid-19 was nonsignificant. However, we need to consider that severe patients receive alternative care, specifically as severe cases are more often hospitalised (Henneghan et al., 2022). Specialist care can include ICU admission and mechanical ventilation, which are associated with impairing cognition, especially in respiratory distress and requiring more extended periods in specialist care (Henneghan et al., 2022). Individuals in specialist care may not undergo cognitive testing or have recovered and become deemed a mild case after discharge (Henneghan et al., 2022). It is also essential to recognise that there may be other underlying mechanisms associated with cognitive function and disease severity. For example, hypoxia may play a critical role in severe cases (Hampshire et al., 2021; Mackowiak et al., 2021). Hypoxia is a potent mechanism underlying cognitive decline after SARS-CoV-2 infection. Brain regions associated with cognitive function, such as the hippocampus, are susceptible to hypoxia-induced neuronal damage. Oxygen deficiency at the acute disease stage and after recovery can cause damages to neurons, which are sensitive to hypoxia (Liu et al., 2021).

Current research on Covid-19 suggests individuals regularly suffer from hypoxia, causing an increased risk of toxic encephalopathy, a type of reversible brain dysfunction syndrome (Alomari et al., 2020). Another risk of Covid-19 occurs when the virus enters lung tissue cells, causing diffuse inflammation oedema, which may lead to hypoxia in the central nervous system, subsequently leading to nervous system damage (Alomari et al., 2020). A further risk is related to an increase in anaerobic metabolism in the mitochondria of brain cells, leading to cerebral vasodilation, swelling of brain cells and obstruction of cerebral blood flow (Alomari et al., 2020). The consequences of this blood flow obstruction can lead to headaches from ischaemia, acute ischemic stroke, and cerebral circulation disorders that have the potential to affect the brain and cognition permanently (Alomari et al., 2020). Various reasons can impact the severity of Covid-19; however, we must iterate that

considering a virus mild or severe differentiates wildly throughout medical practice, deeming the term arbitrary and anecdotal with no definitive, widely accepted definition of severity, conclusions of severity outcomes will differ. Therefore, we suggest that further research on severity is necessary to have a well-informed understanding of how infection may alter cognition and how severity is measured in Covid-19 cases.

The last moderator that was significant was treatment. We found significance in both patients who received treatment and those who did not. These results may suggest that whether an individual had received treatment or not, they may still experience cognitive impairment after recovery from Covid-19. There is currently minimal research regarding the impact of treatment on cognitive impairment after Covid-19 recovery. One study identified that those who received treatment in the emergency department were more likely to have impaired cognition than those in an outpatient setting (Becker et al., 2021). However, it is difficult to make conclusions about the most effective treatment with the least debilitating outcome, specifically during hospitalisation, without long-term data. We refer to the paragraph above where we outline intervention that explains treatment during the severe stages of Covid-19 and how this may impact cognition. The introduction of vaccines, viral treatments, and additional research concerning treatment will begin to explain treatment's effects on cognitive impairment after Covid-19 recovery.

Nonsignificant Moderators

We now turn to the moderators that yielded nonsignificant effects. The two other moderator variables relating to clinical characteristics, strain variants and genetic variants that may predispose individuals to illness**,** did not yield any results in the included studies and were therefore unable to be analysed. The other moderator variables relating to participant characteristics, racial-ethnic groups, age and sex had nonsignificant effects. The

results of age were surprising as the effect was negative and nonsignificant. That age was nonsignificant was contrary to our prediction, but the lack of older and paediatric samples may have reduced the likelihood to detect an effect. Current research on Covid-19 suggests that older adults are at high risk of severe cognitive outcomes associated with comorbidities, chronic illness, and biological predispositions (Hampshire et al., 2021). Older populations may also be at an increased risk of getting a severe illness or even death if they become infected. The weaknesses of advanced age are related to the function of defence cells T and B and the excess production of type 2 cytokines, leading to a prolonged proinflammatory response (Hampshire et al., 2021). Although there is currently no longitudinal data on how Covid-19 impacts older adults' cognition, it is suggested that mechanisms in the inflammatory response associated with Alzheimer's disease resemble processes caused by Covid-19, this information leads to the assumption that older adults are at increased risk of cognitive impairment from the virus (Hampshire et al., 2020; Heneka et al., 2020). Long-term studies are necessary to prove clinical observations, mainly to observe the similarities in the disease pathogenesis of Covid-19 and Alzheimer's disease (Heneka et al., 2020). The 'cytokine storm' of proinflammatory cytokines such as IL-6 and TNF-α observed in Covid-19, in addition to amyloid-beta (Aβ) and phosphorylated tau, resemble processes of the pathogenesis of Alzheimer's disease (Meier et al., 2021). The loss of smell occurs irreversibly in Alzheimer's disease and appears to be transient in Covid-19, hinting at another common pathway (Meier et al., 2021). We anticipated our results to reflect these poor cognitive outcomes; however, few studies examined Covid-19 and cognitive function in older adults without degenerative disease, suggesting this question could be a key avenue for future research.

Current research concerning younger adults suggests that younger populations may be more vulnerable to cognitive outcomes from Covid-19. Cases in younger adult populations

have continued to increase, and although Covid-19 appears less severe in younger adults, this cohort is still at significant risk of Covid-19 neurologic complications (Fifi & Mocco, 2020). Young adulthood is critical for development; individuals seek higher education, establish careers, and become increasingly independent, making this a potentially vulnerable time. It is predicted that post-Covid-19 issues may occur mostly in older adults; however, Covid-19 is predicted to increase the risk of future cognitive impairment in younger adults, too (Alonso-Lana et al., 2020). Early life experiences and exposures increase the risk of dementia in younger adults, as is the case in other risk factors for dementia, such as a low level of education or depression early in life (Fifi & Mocco, 2020). Concerning education, there is a higher likelihood of cognitive impairment among patients with fewer years of education (Valdes et al., 2022). Research suggests that individuals with greater education possess a greater cognitive reserve and capacity to recruit eloquent brain regions (Lenehan et al., 2015), which allows them to sustain a more considerable degree of brain pathology before clinical impairment becomes apparent (Valdes et al., 2022).

That racial-ethnic group was nonsignificant was not surprising considering only two studies (Frontera et al., 2021; Serrano-Castro et al., 2021) reported racial-ethnic data. However, current research suggests that racial-ethnic differences are a predictive factor of Covid-19's influence on cognitive impairment. One study (Valdes et al., 2022) found that the Black race significantly predicts Covid-19 cognitive dysfunction. Research suggests that health disparities, including increased rates of Covid-19 infection, increased mortality, and increased severity of illness, have been associated with racial-ethnic minority groups, particularly in the Black populations (Valdes et al., 2022). Traditionally, health disparities within medicine have been ascribed to differences in medical conditions such as hypertension, kidney disease, and diabetes. However, research shows that these conditions are independent risk factors and are not associated with worsening cognitive scores for Black

populations (Valdes et al., 2022). Biological effects are another possible explanation for why racial-ethnic groups differ with Covid-19 cognitive outcomes. Research on gene-regulating SARS-CoV-2 uptake, endosomal trafficking and cytokine signalling are differentially expressed in Black Americans compared to European White Americans with Covid-19 (Fricke-Galindo & Falfán-Valencia, 2021). These results indicate that Covid-19 cognitive outcomes may be more severe for Black patients than European Whites. Although there is increasing research regarding health disparities among racial-ethnic groups, further research is needed to understand the differences of race and its impact on Covid-19 cognitive outcomes.

Our last nonsignificant moderator was sex differences. Sex differences had no significant moderating effect, suggesting males and females are equally susceptible to cognitive impairment from Covid-19. Covid-19 research indicates that males experience higher mortality and severity than females (Maleki Dana et al., 2020). Studies have outlined that these differences may reflect differences in interactions among immune response and angiotensin-converting enzyme 2 (ACE2) expression related to X inactivation and the effects of sex hormones on these pathways (Henneghan et al., 2022). Research suggests females have increased susceptibility to disorders such as Alzheimer's and depression, but males tend to have poorer cognitive outcomes following neurologic conditions, specifically those involving X chromosome effects (Henneghan et al., 2022). Evolutionary perspectives of sex differences indicate that women have higher baseline performance than men in global cognition, executive function, and memory (Levine et al., 2021). Studies on sex differences have consistently found differences in baseline cognitive functioning, with women demonstrating stronger verbal cognitive skills than men but men demonstrating stronger visuospatial skills than women (Levine et al., 2021). Reasons for these sex differences are complex and likely influenced by biological, genetic, social and cultural factors (Levine et

al., 2021). Fortunately, in SARS-related conditions, increased immune function pertains to enhanced anti-inflammatory regulation and antiviral defence in females and appears to be protective (Thomas et al., 2021). However, the long-term fallout of Covid-19 may be worse for females than for males due to psychosocial, economic, and biological reasons and remains to be explored and revealed (Thomas et al., 2021). Based on previous research, we suggest that caution should be taken when interpreting our results and that further research is necessary to understand the full extent of Covid-19's impact on cognition among sex differences.

Lastly, we turn to the two moderators that we could not analyse due to no data within the included studies; genetic variants and strain variants. Genetic variants refer to genetic predispositions that may impact an individual's cognition for reasons not related to Covid-19, such as neurodegeneration (Meier et al., 2021). Research suggests that genetic variants may play a part in how Covid-19 impacts an individual's cognitive function (Meier et al., 2021). For example, older adults with Apolipoprotein E (ApoE4), a protein involved in the metabolism of fats in the body of mammals, a subtype implicated in Alzheimer's disease (Safieh et al., 2019), are known to undergo more severe Covid-19 than those who do not carry the protein (Meier et al., 2021). ApoE4 e4e4 (high risk of Alzheimer's) homozygotes are more likely to be Covid-19 positive compared to e3e3 (does not influence Alzheimer's risk) homozygotes (Kuo et al., 2020). Another risk of ApoE4 is associated with the increased risk of cardiovascular disease, a common comorbidity observed in individuals with Covid-19 (Meier et al., 2021). ApoE4 is also associated with microbleeds, which disrupts the blood-brain barrier (Meier et al., 2021). In Covid-19, microbleeds increase the risk of ischemia, contributing to cognitive impairment (Meier et al., 2021). These genetic variants may play a crucial part in an individual's susceptibility to having cognitive

impairment after Covid-19; however, with limited data, we will not be able to make specific conclusions on their impact until more research is produced.

Our last moderator that was not analysed is strain variants, and throughout the pandemic, many SARS-CoV-2 variants have appeared (El-Shabasy et al., 2022). There are various reasons mutations occur, specifically, the global absence of immunity and increase replication processes (El-Shabasy et al., 2022). Mutation of SARS-CoV-2 variants may support the viruses' ability for binding with human receptor angiotensin-converting enzyme 2 (ACE2), therefore increasing the spread of the Covid-19 pandemic (El-Shabasy et al., 2022). The Delta variant, which was announced in October 2020, had an advanced rate of transmission and infection compared with other previously known variants (Araf et al., 2022). However, on 9 November 2021, Omicron was discovered and distinguished by the remarkable speed at which it spread, with a transmission rate to be much higher than the pre-existing variants because of the greater number of mutations (Araf et al., 2022). Research suggests that the Omicron variant possesses many mutations in the S protein, which may increase the virus's ability to evade infection-blocking antibodies and other immune responses (Araf et al., 2022). This observation aligns with preliminary evidence suggesting an increased risk of reinfection with Omicron compared to other strains, but the information is still scarce. We suggest that further research on different strains of Covid-19 is essential to understand the association of different variants and their impact on cognitive function.

Although some moderators had a noticeable effect on the relationship between Covid-19 and cognitive function, no single moderator can explain the varying factors involved in Covid-19 and cognitive impairment, demonstrating Covid-19's monumental impact on the population. It is important to question what else might account for this variability? Other factors not included in the current meta-analysis may have had moderating effects, including medication, participant medical history of cognitive difficulties and neurodegenerative

disorders. It may be valuable to examine these other moderating effects to identify other factors involved in driving cognitive impairment. To assess the effect of medication, participant medical history of cognitive difficulties and neurodegeneration would require access to participant-level data or categorising Covid-19 patients into subgroups (such as a history of familial neurodegeneration and no history) not done in the included studies. This situation is a clear example of sharing (deidentified) participant-level data. If this information had been collected and shared in some of the included studies, moderator analyses could have been performed without running additional studies. With online tools such as the Open Science Framework now making it easier to share data, we hope it will be possible to conduct more powerful (and thus more informative) analyses on Covid-19 and cognitive function in the coming years. Finally, given the various measuring instruments used to identify aspects of cognitive function (Montreal Cognitive Assessment, Cognitive Impairment in Psychiatry Danish Version, Telephone Instrument for Cognitive Status, and Cognition), there were likely subtle differences between the tasks not captured by the current coding of methodological moderator variables.

Cognitive Domains

Based on the reported evidence, it appears that patients experience varying degrees of cognitive impairment after Covid-19 infection. Our results reflect this evidence and demonstrate deficits in attention, memory, and executive functions. This pattern of impairment is consistent with current research describing dysexecutive syndrome after Covid-19 and has considerable implications for psychological, occupational, and functional outcomes (Alonso-Lana et al., 2020; Becker et al., 2021). As more research explores the consequences of Covid-19, the nature of sustained cognitive impairment during and after the recovery era becomes more apparent. Early estimates of neurological and cognitive

impairments in approximately one-third of Covid-19 survivors have been replicated (Yates, 2021; Mao et al., 2020; Beaud et al., 2021). Although, inconsistencies in study populations and definitions of cognitive or neurological impairment has resulted in some reports of cognitive deficits in up to 75-80% of Covid-19 survivors (Yates, 2021; Mao et al., 2020; Beaud et al., 2021). Research suggests that mixed populations, such as younger and older populations, are now at risk of domain-specific impairment and may be particularly susceptible to cognitive impairment after a critical illness from Covid-19 (Alonso-Lana et al., 2020). Neuroimaging research suggests the involvement of brain regions relevant to executive control processes, including the prefrontal cortex, parietal cortex, cingulate cortex, and striatum (Uddin, 2021). Current research indicates that attention, executive function and working memory are at the highest risk of impairment, as evident in our results (Becker et al., 2021; Hampshire et al., 2021). The detailed profile and extent of cognitive impairment in Covid-19 survivors are not yet clear, in part due to inconsistencies across studies of the cognitive domains assessed; therefore, further research is required to establish a more informed understanding of Covid-19's impact on specific cognitive domains.

The global cognitive screening tools used in the included studies was the MoCA (n = 7), followed by TICS-M (n = 1), SCIP-D (n=1) and the Cognitrone (n = 1). Comparing patient populations with different instruments, each with different sensitivity and specificity, could explain the variance of results. Amongst cognitive domains, executive functioning, attention, and memory, are associated with inflammation and hypoxia symptoms, often reported with Covid-19 outcomes (Ceban et al., 2021). Our results provide the importance of further research into cognitive domains to establish targeted interventions after Covid-19. Given the prevalence of Covid-19, targeting these deficits would be beneficial and may support optimal cognitive and functional outcomes. The results of this meta-analysis suggest that patients who have recently recovered from Covid-19 may experience global cognitive

impairment and often a reduction in executive functions, attention, and memory. This indicates that some Covid-19 recovered patients may benefit from tailored cognitive support, including cognitive rehabilitation therapy or cognitive-motor training. Additional research is required to identify the underlying mechanisms of Covid-19, develop standardised criteria, and establish effective therapies. Controlled study designs and standardised assessment tools are valuable to understand the causal relationship of Covid-19 and its impact on cognitive function. It will also be beneficial to study more detailed medical and social consequences of Covid-19 to have a well-informed understanding of different dynamics in communities and assist in rehabilitation and treatment plans. Lastly, valid and reliable data is also needed to investigate the longer-term impact of Covid-19 on cognition.

Limitations and Future Research

We should point out a few limitations to the present meta-analysis. First, preliminary studies for some moderator categories meant that we did not have sufficient data to understand the capacity to which Covid-19 affects cognitive function. Particularly notable is the lack of research in lower socioeconomic communities. It is presumed that those of lower socioeconomic groups are at higher risk of exposure because they have less opportunity to follow spread-prevention norms than people of higher social status (Oishi et al., 2021; von Braun et al., 2020; Weill et al., 2020). Current research on the Covid-19 outbreak assumes that individuals of lower social status may be exposed to the virus due to work conditions, lack of education, lack of financial resources and living in crowded conditions (Yi et al., 2021). For these reasons, the idea that those living in lower socioeconomic communities are at higher risk of contracting Covid-19 is not understood as a universal rule (Patel et al., 2020). We highlight the importance of future studies addressing this research gap to ensure that various communities produce accurate outcomes. Second, it is essential to note that the

lack of regional differences in research may skew the results of this meta-analysis. Notably, most of the studies in this research are from eurocentric, WEIRD (western, educated, industrialised, rich, democratic) societies, which can lead to demographic bias and does not give researchers the ability to have a universal understanding of Covid-19's impact on cognitive function. Similarly, most studies were based on hospitalised individuals. The studies did not point out the different demographics of the healthcare system within the community, which may not represent the majority of individuals affected by Covid-19. This may lead to selection bias, with an overrepresentation of hospitalised cases who may have comorbid conditions, be on medication or have post-intensive care syndrome (Ceban et al., 2021). Another limitation is that most studies used dementia screening tools (e.g., TICS, MoCA); these tools may have limited sensitivity to younger populations and may lead to underestimating cognitive impairment (McIntyre et al., 2019). We recommend that future studies use cognitive tools devoid of ceiling effects, for example, the Screen for Cognitive Impairment for Psychiatry (SCIP) (Miskowiak et al., 2021). Lastly, due to the rapidly evolving situation of Covid-19, many regions affected have yet to publish clinical datasets, which may skew the results of this analysis.

APPENDICES

Table 1

Literature search terms. To be included, studies will need to mention at least one term from each column (i.e., Covid-19 AND Cognition).

Covid-19	Cognition
Covid-19	Cognition
Sars-cov-2	Cognitive
Coronavirus	Cognitive function
Covid	Cognitive impairment
2019-cov	Cognitive changes
Corona	Cognitive performance
B.1.526.1	Cognitive status
B.1.1.7	Cognitive dysfunction
B.1.351	Cognitive deficit
P.1	Cognitive decline
B.1.427	Executive
B.1.429	Executive function
B.1.617	Cognitive assessment
B.1.526	Neuro*
P.2	Brain*
B.1.525	Cog*
nCoV 19	
nCoV19	
Covid19	
Covid 19	
SARSCoV2	
SARSCoV-2	
New CoV	
novel CoV	
SARS coronavirus2	
SARS coronavirus 2	
Coronavirus 19	
Coronavirus19	

Table 4

Designs, Moderators, and Variables of Included Studies

Author	Study	Study Design	Moderators	Number of Effect Sizes	Female/Male Percentage	Outcome Measures	Covid Severity	Cognitive Domains Obsevered
Frontera et al. (2021)	1	Prospective study of long-term outcomes among hospitalised Covid-19 patients.	Race/ethnicity, sex, regional differences, disease severity, treatment, comorbidity.	1	Female; 35%. Male; 65%.	MoCA	Mild	NA
Miskowiak et al. (2021)	2	Prospective study examining all patients admitted to hospital acutely for Covid-19.	Age, sex, regional differences, disease severity, comorbidity.	1	Female; 41%. Male; 59%.	SCIP-D	Severe	Memory, executive function, attention
Raman et al. (2020)	3	Prospective observational cohort study including patients with moderate to severe Covid-19.	Race/ethnciity, age, sex, regional differences, disease severity, treatment, comorbidity.	1	Female; 41.4%. Male; 58.6%.	MoCA	Severe	Executive function
Woo et al. (2020)	4	Cross-sectional study involving patients from an outpatient clinic.	Age, sex, regional differences, disease severity, treatment, comorbidity.	1	Female; 57.9%. Male; 42.1%.	TICS-m	Mild	Attention, executive function, memory
Blazhenets et al. (2021)	5	Prospective study examining patients on a monocentric register who required inpatient treatment.	Regional differences, disease severity, treatment, comorbidity.	1	NA	MoCA-G	Severe	Executive function, memory
Del Brutto et al. (2020)	6	Longitudinal prospective study nested to a population cohort on cognitive decline among Covid-19 positive patients.	Age, sex, regional differences, disease severity.	1	Female; 63%. Male; 37%.	MoCA	Mild	NA
Pirker-Kees et al. (2021)	7	Experimental study involving participants from an inpatient unit.	Age, sex, regional differences, disease severity.	1	Female; 42.9%. Male; 57.1%.	MoCA	Mild	NA
Triana et al. (2020)	8	Retrospective cohort study examining inpatients against healthy controls.	Age, sex.	1	Female; 52.38%. Male; 47.62%.	MoCA	NA	Attention, memory
Delgado-Alonso et al. (2021)	9	Cross-sectional study involving patients with Covid-19 reporting	Age, sex, treatment, comorbidity.	1	Female; 74%. Male; 26%.	Cognitrone	NA	NA

		cognitive complaints at least three months after the onset of the disease.						
Serrano-Castro et al. (2021)	10	Cross-sectional study of patients who survived severe infection with SARS-CoV-2.	Race/ethnicity, age, sex, regional differences, disease severity, treatment, comorbidity.	1	Female; 63.04%. Male 36.95%.	MoCA	Severe	NA

Note. MoCA = Montreal Cognitive Assessment; SCIP-D = Cognitive Impairment in Psychiatry Danish Version; TICS-m = Telephone Instrument for Cognitive Status; MoCA-G = Montreal Cognitive Assessment German Version.

Table 7

Study Quality

Article Name and Author: Study 1	A prospective study of long-term outcomes among hospitalised COVID-19 patients with and without neurological complications	Frontera et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 2	Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables	Miskowiak et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 3	Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge	Raman et al. (2020)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	

Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 4	Frequent neurocognitive deficits after recovery from mild COVID-19	Woo et al. (2020)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 5	Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients	Blazhenets et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14

Article Name and Author: Study 6	Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort	Del Brutto et al. (2020)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	Yes	14/14

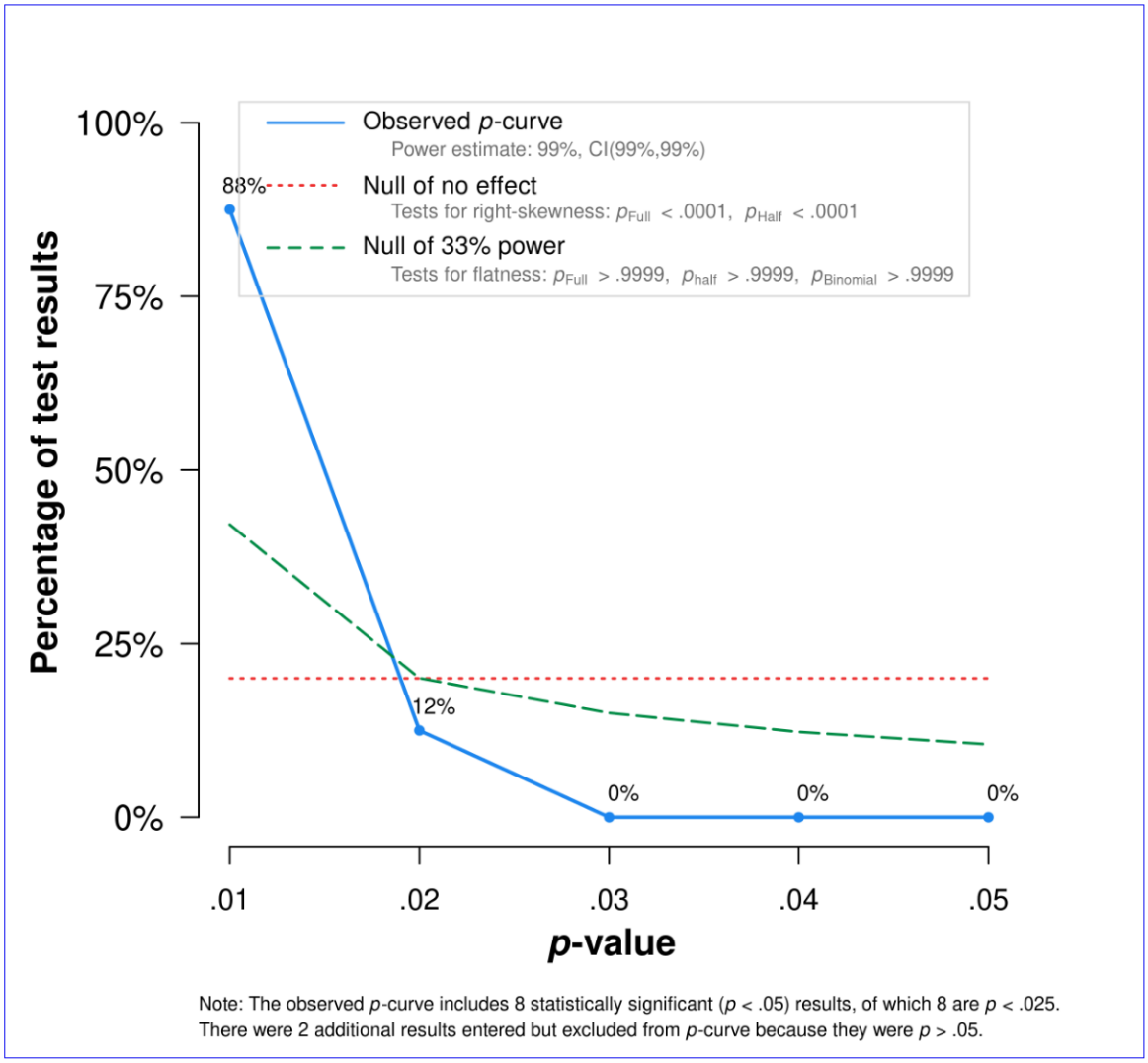
Article Name and Author: Study 7	Hyposmia is associated with reduced cognitive function in COVID-19: First preliminary results	Pirker-Kees et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	No	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	12/14

Article Name and Author: Study 8	Cognitive performance in convalescent COVID-19 patients	Triana et al. (2020)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	

Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 9	Cognitive dysfunction associated with COVID-19: a comprehensive neuropsychological study	Delgado-Alonso et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	No	13/14
Article Name and Author: Study 10	The cognitive and psychiatric subacute impairment in severe Covid-19	Serrano-Castro et al. (2021)
Study hypothesis/aim/objective described?	Yes	
Main outcomes described in the introduction or methods?	Yes	
Participant characteristics described?	Yes	
Contacted participants representative?	NA	
Prepared participants representative?	NA	
Participants recruited from the same population?	Yes	
Participants recruited over the same time?	Yes	
Measures and experimental tasks described?	Yes	
Main outcome measures valid and reliable?	Yes	
Task engagement assessed?	NA	
Confounders described and controlled for?	Yes	
Statistical tests appropriate?	Yes	
Main findings described?	Yes	
Estimates of the random variability in data main outcomes?	Yes	
Probability values reported?	Yes	
Withdrawals and drop-outs reported?	Yes	
Data dredging made clear?	NA	
Sufficient power analysis provided?	Yes	14/14

Figure 6

P-curve of Included Effect Sizes



Note. P-curve of included effect sizes that were statistically significant (generated from P-curve.com). The right-skew of the observed *p*-curve (blue) suggests there is no evidence the included effect sizes were subject to publication and/or reporting bias.

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