# Appendix A

Appended to Implications for systemic approaches to COVID-19: effect sizes of Remdesivir, Tocilizumab, melatonin, vitamin D3, and meditation

Submission ID: 323356

Populations covered in the included studies often tracked the effects of catalysts on markers within specific groups. For the purposes of tracking broad patterns the results were averaged for this article’s analysis, but in the event discrete effect sizes could be valuable they are included in this Appendix.

One of the justifications for averaging effect sizes was the highly heterogeneous nature of time intervals and duration of intervention. The effects of several interventions were tracked during multiple check in (intvn Tx), but these time frames ranged across studies from several days to one year after initial administration (T1). Tracking of COVID-19 effects was largely after admission to a hospital, which leads to implications discussed in the Limitations section.

The research results that were reviewed, computed, and analyzed include the following:

* **Aiswarya 202153**
* **Akbari 202054**
* **Alamdari 201555**
* **Bartels 201356**
* **Bower 201557**
* **Cahn 201758**
* **Carlson 200359**
* **Carlson 200460**
* **Carlson 200761**
* **Celinski 201462**
* **Chen 202063,64**
* **Cichoz-Lach 201065**
* **Epel 201666**
* **Gonzalez-Garcia 201467**
* **Javanmard 201668**
* **Lengacher 201369**
* **Qin 202070,71**
* **Rausch-Fan 200272**
* **Raygan 201973**
* **Rosenkranz 201674**
* **Shete 201775**
* **Smolen 200876**
* **Wang 202077**
* **Witek-Janusek 200878**
* **Zhang 202079**

### COVID-19

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Akbari 2020 | COVID 19 | CD19 | CoV2 General | wmd to smd approx | reg | -2.043026 |
| Akbari 2020 | COVID 19 | CD4 | CoV2 General | wmd to smd approx | reg | -4.44223 |
| Chen 2020 | COVID 19 | CD4 | CoV2 General | approx SMD | reg | -0.575 |
| Akbari 2020 | COVID 19 | CD8 | CoV2 General | wmd to smd approx | reg | -3.652707 |
| Chen 2020 | COVID 19 | CD8 | CoV2 General | approx SMD | reg | -1.452736 |
| Wang 2020 | COVID 19 | CRP | CoV2 General | approx SMD | dys | 2.4705882 |
| Akbari 2020 | COVID 19 | CRP | CoV2 General | wmd to smd approx | dys | 2.5677167 |
| Qin 2020 | COVID 19 | CRP | CoV2 General | approx SMD | dys | 4.4151899 |
| Qin 2020 | COVID 19 | Eosinophil | CoV2 General | approx SMD | reg | -4.2 |
| Akbari 2020 | COVID 19 | ESR | CoV2 General | wmd to smd approx | dys | 2.4039575 |
| Wang 2020 | COVID 19 | ESR | CoV2 General | approx SMD | dys | 2.9333333 |
| Qin 2020 | COVID 19 | ESR | CoV2 General | approx SMD | dys | 3.4285714 |
| Akbari 2020 | COVID 19 | Ferritin | CoV2 General | wmd to smd approx | dys | 2.6910769 |
| Chen 2020 | COVID 19 | IL-10 | CoV2 General | approx SMD | reg | -1.578475 |
| Qin 2020 | COVID 19 | IL-10 | CoV2 General | approx SMD | reg | 0.4927536 |
| Akbari 2020 | COVID 19 | IL-2 | CoV2 General | wmd to smd approx | reg | 2.1998878 |
| Akbari 2020 | COVID 19 | IL-4 | CoV2 General | wmd to smd approx | dys | 0.9642365 |
| Wang 2020 | COVID 19 | IL-6 | CoV2 General | approx SMD | dys | 2.5333333 |
| Qin 2020 | COVID 19 | IL-6 | CoV2 General | approx SMD | dys | 2.9106029 |
| Akbari 2020 | COVID 19 | IL-6 trans | CoV2 General | wmd to smd approx | dys | 3.5484992 |
| Qin 2020 | COVID 19 | IL-8 | CoV2 General | approx SMD | dys | -1.451777 |
| Akbari 2020 | COVID 19 | IL-8 | CoV2 General | wmd to smd approx | dys | 0.8907709 |
| Chen 2020 | COVID 19 | INF-λ | CoV2 General | approx SMD | reg | -1.651148 |
| Akbari 2020 | COVID 19 | INF-λ | CoV2 General | wmd to smd approx | reg | 1.4647212 |
| Akbari 2020 | COVID 19 | Lymphocytes | CoV2 General | wmd to smd approx | reg | -4.141625 |
| Wang 2020 | COVID 19 | Lymphocytes | CoV2 General | approx SMD | reg | -4 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 General | approx SMD | reg | -3.703704 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 General | approx SMD | reg | -3.153153 |
| Chen 2020 | COVID 19 | Lymphocytes | CoV2 General | approx SMD | reg | -1.042084 |
| Akbari 2020 | COVID 19 | Monocyte | CoV2 General | wmd to smd approx | dys | -0.064282 |
| Qin 2020 | COVID 19 | Monocyte | CoV2 General | approx SMD | dys | 0.4102564 |
| Qin 2020 | COVID 19 | NK cell | CoV2 General | approx SMD | reg | -3.077355 |
| Akbari 2020 | COVID 19 | NK cell | CoV2 General | wmd to smd approx | reg | -2.296653 |
| Qin 2020 | COVID 19 | Th Memory cells | CoV2 General | approx SMD | reg | 0.2378378 |
| Qin 2020 | COVID 19 | Th Naïve cells | CoV2 General | approx SMD | reg | -0.172727 |
| Akbari 2020 | COVID 19 | TNF a | CoV2 General | wmd to smd approx | dys | 0.7378506 |
| Qin 2020 | COVID 19 | TNF a | CoV2 General | approx SMD | dys | 3.0082645 |
| Chen 2020 | COVID 19 | CD4 | CoV2 Mild | approx SMD | reg | -0.638037 |
| Chen 2020 | COVID 19 | CD8 | CoV2 Mild | approx SMD | reg | -0.851485 |
| Qin 2020 | COVID 19 | CRP | CoV2 Mild | approx SMD | dys | 4.9828571 |
| Qin 2020 | COVID 19 | Eosinophil | CoV2 Mild | approx SMD | reg | -3.855422 |
| Qin 2020 | COVID 19 | ESR | CoV2 Mild | approx SMD | dys | 3.2156863 |
| Chen 2020 | COVID 19 | IL-10 | CoV2 Mild | approx SMD | reg | -1.520362 |
| Qin 2020 | COVID 19 | IL-10 | CoV2 Mild | approx SMD | reg | 0.3243243 |
| Qin 2020 | COVID 19 | IL-6 | CoV2 Mild | approx SMD | dys | 1.7737557 |
| Qin 2020 | COVID 19 | IL-8 | CoV2 Mild | approx SMD | dys | -1.867746 |
| Chen 2020 | COVID 19 | INF-λ | CoV2 Mild | approx SMD | reg | -0.813232 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 Mild | approx SMD | reg | -3.407407 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 Mild | approx SMD | reg | -2.305085 |
| Chen 2020 | COVID 19 | Lymphocytes | CoV2 Mild | approx SMD | reg | 0.3235955 |
| Qin 2020 | COVID 19 | Monocyte | CoV2 Mild | approx SMD | dys | 1.3451327 |
| Qin 2020 | COVID 19 | NK cell | CoV2 Mild | approx SMD | reg | -2.831557 |
| Qin 2020 | COVID 19 | Th Memory cells | CoV2 Mild | approx SMD | reg | 0.8690196 |
| Qin 2020 | COVID 19 | Th Naïve cells | CoV2 Mild | approx SMD | reg | -0.76 |
| Qin 2020 | COVID 19 | TNF a | CoV2 Mild | approx SMD | dys | 3 |
| Chen 2020 | COVID 19 | CD4 | CoV2 Severe | approx SMD | reg | -0.601307 |
| Chen 2020 | COVID 19 | CD8 | CoV2 Severe | approx SMD | reg | -2.567639 |
| Qin 2020 | COVID 19 | CRP | CoV2 Severe | approx SMD | dys | 5.512605 |
| Qin 2020 | COVID 19 | Eosinophil | CoV2 Severe | approx SMD | reg | -4.307692 |
| Qin 2020 | COVID 19 | ESR | CoV2 Severe | approx SMD | dys | 3.7857143 |
| Chen 2020 | COVID 19 | IL-10 | CoV2 Severe | approx SMD | reg | -1.513978 |
| Qin 2020 | COVID 19 | IL-10 | CoV2 Severe | approx SMD | reg | 1.0649351 |
| Qin 2020 | COVID 19 | IL-6 | CoV2 Severe | approx SMD | dys | 3.3384615 |
| Qin 2020 | COVID 19 | IL-8 | CoV2 Severe | approx SMD | dys | -1.274336 |
| Chen 2020 | COVID 19 | INF-λ | CoV2 Severe | approx SMD | reg | -2.928975 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 Severe | approx SMD | reg | -4.153846 |
| Qin 2020 | COVID 19 | Lymphocytes | CoV2 Severe | approx SMD | reg | -3.924883 |
| Chen 2020 | COVID 19 | Lymphocytes | CoV2 Severe | approx SMD | reg | -2.250591 |
| Qin 2020 | COVID 19 | Monocyte | CoV2 Severe | approx SMD | dys | 0.0695652 |
| Qin 2020 | COVID 19 | NK cell | CoV2 Severe | approx SMD | reg | -3.310702 |
| Qin 2020 | COVID 19 | Th Memory cells | CoV2 Severe | approx SMD | reg | -0.129877 |
| Qin 2020 | COVID 19 | Th Naïve cells | CoV2 Severe | approx SMD | reg | 0.2235294 |
| Qin 2020 | COVID 19 | TNF a | CoV2 Severe | approx SMD | dys | 2.952381 |

*Table A1: CoV2 General tracks the effect size on that marker within an undifferentiated group of those infected with COVID-19. CoV2 Mild tracks the effect size on that marker within a group demonstrating mild COVID-19 symptoms. CoV2 Mild tracks the effect size on that marker within a group demonstrating severe COVID-19 symptoms. ES Format= method for determining effect size. Approx SMD= effect size determined using test metrics, control metrics, and pooled standard deviations and/or test-n, control-n, and a minimum/maximum range of reported values. WMD to SMD Approx= weight mean difference converted to standardized mean difference using the WMD value, n, the minimum/maximum range of reported values, and the SD. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

### Vitamin D3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Bartels 2013 | D3 | IL-10 | Intvn T1 | approx SMD | reg | -0.394619 |
| Bartels 2013 | D3 | IL-6 classic | Intvn T1 | approx SMD | reg | 0.7721088 |
| Rausch-Fan 2002 | D3 | IL-6 trans | Intvn T1 | approx SMD | dys | -1.651685 |
| Rausch-Fan 2002 | D3 | TNF a | Intvn T1 | approx SMD | dys | -2.645161 |
| Bartels 2013 | D3 | TNF a | Intvn T1 | approx SMD | dys | -1.582645 |

*Table A2: Descriptions with times= interventions were regularly administered at this time. Intvn T1= effect in first tracked measurement after intervention. ES Format= method for determining effect size. Approx SMD= effect size determined using test metrics, control metrics, and pooled standard deviations and/or test-n, control-n, and a minimum/maximum range of reported values. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

### Meditation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Carlson 2004 | Meditation | Cortisol | 2pm | approx SMD | dys | -0.149 |
| Witek Janusek 2008 | Meditation | Cortisol | 4-6pm | approx SMD | dys | -0.572 |
| Carlson 2007 | Meditation | CD19 | Intvn T1 | approx SMD | reg | 0.04 |
| Carlson 2007 | Meditation | CD3 | Intvn T1 | approx SMD | reg | -0.038 |
| Carlson 2007 | Meditation | CD4 | Intvn T1 | approx SMD | reg | -0.098 |
| Gonzalez-Garcia 2013 | Meditation | CD4 | Intvn T1 | approx SMD | reg | 0.56 |
| Carlson 2007 | Meditation | CD8 | Intvn T1 | approx SMD | reg | -0.041 |
| Rosenkranz 2016 | Meditation | Cortisol | Intvn T1 | approx SMD | dys | -1.509728 |
| Carlson 2003 | Meditation | Eosinophil | Intvn T1 | approx SMD | reg | 0.31 |
| Carlson 2003 | Meditation | IL-10 | Intvn T1 | approx SMD | reg | -0.375 |
| Carlson 2007 | Meditation | IL-10 | Intvn T1 | approx SMD | reg | -0.231 |
| Witek Janusek 2008 | Meditation | IL-10 | Intvn T1 | approx SMD | reg | 0.309 |
| Carlson 2003 | Meditation | IL-4 | Intvn T1 | approx SMD | dys | -1.007 |
| Witek Janusek 2008 | Meditation | IL-4 | Intvn T1 | approx SMD | dys | -0.459 |
| Carlson 2007 | Meditation | IL-4 | Intvn T1 | approx SMD | dys | -0.004 |
| Shete 2017 | Meditation | IL-6 | Intvn T1 | approx SMD | dys | -0.941176 |
| Witek Janusek 2008 | Meditation | IL-6 | Intvn T1 | approx SMD | dys | -0.571 |
| Bower 2015 | Meditation | IL-6 | Intvn T1 | approx SMD | dys | -0.2 |
| Cahn 2017 | Meditation | IL-6 classic | Intvn T1 | approx SMD | reg | 0.5820896 |
| Carlson 2003 | Meditation | INF-λ | Intvn T1 | approx SMD | reg | -0.33 |
| Carlson 2007 | Meditation | INF-λ | Intvn T1 | approx SMD | reg | -0.004 |
| Carlson 2007 | Meditation | Lymphocytes | Intvn T1 | approx SMD | reg | 0.169 |
| Carlson 2003 | Meditation | Monocyte | Intvn T1 | approx SMD | dys | -0.293 |
| Witek Janusek 2008 | Meditation | NK cell | Intvn T1 | approx SMD | reg | 0.472 |
| Lengacher 2013 | Meditation | Th Memory cells | Intvn T1 | approx SMD | reg | 0.5612648 |
| Epel 2016 | Meditation | TNF a | Intvn T1 | approx SMD | dys | -1.407407 |
| Shete 2017 | Meditation | TNF a | Intvn T1 | approx SMD | dys | -1.042553 |
| Carlson 2007 | Meditation | TNF a | Intvn T1 | approx SMD | dys | -0.098 |
| Carlson 2007 | Meditation | CD19 | Intvn T2 | approx SMD | reg | 0.193 |
| Carlson 2007 | Meditation | CD3 | Intvn T2 | approx SMD | reg | -0.0309 |
| Carlson 2007 | Meditation | CD4 | Intvn T2 | approx SMD | reg | 0.122 |
| Gonzalez-Garcia 2013 | Meditation | CD4 | Intvn T2 | approx SMD | reg | 1.3 |
| Carlson 2007 | Meditation | CD8 | Intvn T2 | approx SMD | reg | -0.239 |
| Carlson 2007 | Meditation | IL-10 | Intvn T2 | approx SMD | reg | -0.073 |
| Carlson 2007 | Meditation | IL-4 | Intvn T2 | approx SMD | dys | -1.014 |
| Carlson 2007 | Meditation | INF-λ | Intvn T2 | approx SMD | reg | -1.235 |
| Carlson 2007 | Meditation | Lymphocytes | Intvn T2 | approx SMD | reg | 0.183 |
| Carlson 2007 | Meditation | TNF a | Intvn T2 | approx SMD | dys | -1.064 |
| Carlson 2007 | Meditation | CD19 | Intvn T3 | approx SMD | reg | 0.215 |
| Carlson 2007 | Meditation | CD3 | Intvn T3 | approx SMD | reg | -0.279 |
| Carlson 2007 | Meditation | CD4 | Intvn T3 | approx SMD | reg | 0.029 |
| Carlson 2007 | Meditation | CD8 | Intvn T3 | approx SMD | reg | -0.24 |
| Carlson 2007 | Meditation | IL-10 | Intvn T3 | approx SMD | reg | -0.105 |
| Carlson 2007 | Meditation | IL-4 | Intvn T3 | approx SMD | dys | -1.835 |
| Carlson 2007 | Meditation | INF-λ | Intvn T3 | approx SMD | reg | -1.291 |
| Carlson 2007 | Meditation | Lymphocytes | Intvn T3 | approx SMD | reg | 0.103 |
| Carlson 2007 | Meditation | TNF a | Intvn T3 | approx SMD | dys | -1.463 |

*Table A3: Descriptions with times= interventions were regularly administered at this time. Intvn T1= effect in first tracked measurement after intervention. Intvn T2= effect in second tracked measurement after intervention (time intervals vary). Intvn T3= effect in third tracked measurement after intervention (time intervals vary). ES Format= method for determining effect size. Approx SMD= effect size determined using test metrics, control metrics, and pooled standard deviations and/or test-n, control-n, and a minimum/maximum range of reported values. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

### Melatonin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Javanmard 2016 | Melatonin | CRP | Intvn T1 | SMD | dys | -3.03 |
| Pakravan 2017 | melatonin | CRP | Intvn T1 | SMD | dys | -2.81 |
| Raygan 2017 | Melatonin | CRP | Intvn T1 | SMD | dys | -1.64 |
| Alamdari 2014 | Melatonin | CRP | Intvn T1 | SMD | dys | 0.22 |
| Alamdari 2014 | Melatonin | IL-6 | Intvn T1 | SMD | dys | -3.54 |
| Celinski 2014 | Melatonin | IL-6 | Intvn T1 | SMD | dys | -1.99 |
| Cichoz-Lach 2010 | Melatonin | IL-6 | Intvn T1 | SMD | dys | -0.62 |
| Celinski 2014 | Melatonin | TNF a | Intvn T1 | SMD | dys | -3.58 |
| Alamdari 2014 | Melatonin | TNF a | Intvn T1 | SMD | dys | -2.03 |
| Cichoz-Lach 2010 | Melatonin | TNF a | Intvn T1 | SMD | dys | -0.06 |

*Table A4: Descriptions with times= interventions were regularly administered at this time. Intvn T1= effect in first tracked measurement after intervention. ES Format= method for determining effect size. SMD= standardized mean differences provided directly by original cited studies. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

### Remdesivir

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Aiswarya 2021 | Remdesivir | CRP | less than 48 hrs | approx SMD | dys | -2.828047 |
| Aiswarya 2021 | Remdesivir | CRP | Intvn T1 | approx SMD | dys | -3.481227 |
| Aiswarya 2021 | Remdesivir | Ferritin | Intvn T1 | approx SMD | dys | 0.010854 |
| Wang, Zhang 2020 | Remdesivir | Lymphocytes | Intvn T1 | approx SMD | reg | 0.7272727 |
| Aiswarya 2021 | Remdesivir | CRP | more than 48 hours | approx SMD | dys | -3.715179 |

*Table A5: Descriptions with hrs= how many hours passed after admission to hospital before intervention was administered. Intvn T1= effect in first tracked measurement after intervention. ES Format= method for determining effect size. Approx SMD= effect size determined using test metrics, control metrics, and pooled standard deviations and/or test-n, control-n, and a minimum/maximum range of reported values. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

### Tocilizumab

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Description | ES Format | Reg or Dys | Effect |
| Smolen 2008 | Tocilizumab | CRP | 4mg | approx SMD | dys | 0.1290323 |
| Smolen 2008 | Tocilizumab | ESR | 4mg | approx SMD | dys | -0.018832 |
| Smolen 2008 | Tocilizumab | CRP | 8mg | approx SMD | dys | 0.0740741 |
| Smolen 2008 | Tocilizumab | ESR | 8mg | approx SMD | dys | 0.0567108 |

*Table A6: Descriptions with mg= dosage of intervention administered. ES Format= method for determining effect size. Approx SMD= effect size determined using test metrics, control metrics, and pooled standard deviations and/or test-n, control-n, and a minimum/maximum range of reported values. Reg= estimated indication of regulatory effect. Dys= estimated indication of dysregulatory effect.*

## Standard mean difference calculation and approximation

*Table A7* includes breakdowns of the values and data extrapolated from the chosen studies that were used to calculate effect sizes via standard mean difference.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Delta Mech | *d 1* | *d 2* | *d 3* | n1 | n2 | n3 | p | *Control SD* | *SD1* | *SD2* | *SD3* | *Control x̅* | CRMin | CR Max | x̅1 | x̅2 | x̅3 | R1 min | R1 max | R2 min | R2 max | R3 min | R3 max |
| Carlson 2007 | Meditation | Lymphocytes overall | SMD | *0.169* | *0.183* | *0.103* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | CD3 % lymph | SMD | *0.038* | *0.0309* | *0.279* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | CD4 | SMD | *0.098* | *0.122* | *0.029* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | CD8 % lymph | SMD | *0.041* | *0.239* | *0.24* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | CD19 % lymph | SMD | *0.04* | *0.193* | *0.215* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | INF-λ | SMD | *0.004* | *1.235* | *1.291* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | TNF a | SMD | *0.098* | *1.064* | *1.463* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | IL-4 | SMD | *0.004* | *1.014* | *1.835* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2007 | Meditation | IL-10 | SMD | *0.231* | *0.073* | *0.105* |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2004 | Meditation | Cortisol 2pm | SMD | *0.149* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2003 | Meditation | Monocyte | SMD | *0.293* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2003 | Meditation | Eosinophil % WBC | SMD | *0.31* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2003 | Meditation | INF-λ | SMD | *0.33* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2003 | Meditation | IL-4 % lymph | SMD | *1.007* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Carlson 2003 | Meditation | IL-10 NK % lymph | SMD | *0.375* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Witek Janusek 2008 | Meditation | NK cell activity | SMD | *0.472* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Witek Janusek 2008 | Meditation | IL-4 | SMD | *0.459* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Witek Janusek 2008 | Meditation | IL-6 | SMD | *0.571* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Witek Janusek 2008 | Meditation | IL-10 | SMD | *0.309* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Witek Janusek 2008 | Meditation | Cortisol 4-6pm | SMD | *0.572* |  |  |   |   |   |   |  |  |  |  |  |   |   |   |   |   |   |   |   |   |   |   |
| Gonzalez-Garcia 2013 | Meditation | CD4 | approx SMD | *0.56* | *1.3* |  |   |   |   | 0.05 | *198* | *183* | *196* | *0* | *555* |   |   | 614 | 681 |   |   |   |   |   |   |   |
| Rosenkranz 2016 | Meditation | Cortisol | approx SMD | *-1.509727626* |  |  |   |   |   | 0.05 | *7.76* | *2.52* |  |  | *70.38* |   |   | 62.62 |   |   |   |   |   |   |   |   |
| Lengacher 2013 | Meditation | Memory Th cells | approx SMD | *0.561264822* |  |  |   |   |   | 0.002 | *11.2* | *14.1* |  |  | *20.9* |   |   | 28 |   |   |   |   |   |   |   |   |
| Cahn 2017 | Meditation | IL-6 classic | approx SMD | *0.582089552* |  |  |   |   |   | 1E-04 | *0.59* | *0.75* | *0* | *0* | *0.79* |   |   | 1.18 |   |   |   |   |   |   |   |   |
| Epel 2016 | Meditation | TNF a | approx SMD | *-1.407407407* |  |  |   |   |   | 0.03 | *0.16* | *0.11* |  |  | *2.51* |   |   | 2.32 |   |   |   |   |   |   |   |   |
| Shete 2017 | Meditation | IL-6 | approx SMD | *-0.941176471* |  |  |   |   |   | 1E-05 | *0.9* | *0.8* |  |  | *2.1* |   |   | 1.3 |   |   |   |   |   |   |   |   |
| Shete 2017 | Meditation | TNF a | approx SMD | *-1.042553191* |  |  |   |   |   | 1E-04 | *7.1* | *11.7* |  |  | *36.9* |   |   | 27.1 |   |   |   |   |   |   |   |   |
| Bower 2015 | Meditation | IL-6 | approx SMD | *-0.2* |  |  | 52 |   |   | 0.158 | *0.63* | *0.67* |  |  | *1.32* |   |   | 1.19 |   |   |   |   |   |   |   |   |
| Qin 2020 | COVID 19 | Lymphocytes overall | approx SMD | *-3.703703704* | *-3.407407407* | *-4.153846154* | 452 | 166 | 286 | 0.001 | *0.525* | *0.15* | *0.15* | *0.125* | *2.15* | 1.1 | 3.2 | 0.9 | 1 | 0.8 | 0.6 | 1.2 | 0.7 | 1.3 | 0.6 | 1.1 |
| Qin 2020 | COVID 19 | Lymphocyte % WBC | approx SMD | *-3.153153153* | *-2.305084746* | *-3.924882629* | 452 | 166 | 286 | 0.001 | *7.5* | *3.6* | *4.3* | *3.15* | *35* | 20 | 50 | 17.5 | 21.4 | 14.1 | 10.7 | 25.1 | 15.3 | 32.5 | 8.8 | 21.4 |
| Qin 2020 | COVID 19 | Monocyte | approx SMD | *0.41025641* | *1.345132743* | *0.069565217* | 452 | 166 | 286 | 0.001 | *1.75* | *1.175* | *1.075* | *1.125* | *6.5* | 3 | 10 | 7.1 | 8.4 | 6.6 | 4.9 | 9.6 | 6.5 | 10.8 | 4.3 | 8.8 |
| Qin 2020 | COVID 19 | Eosinophil % WBC | approx SMD | *-4.2* | *-3.855421687* | *-4.307692308* | 452 | 166 | 286 | 0.001 | *1.9* | *0.1* | *0.175* | *0.05* | *4.2* | 0.4 | 8 | 0 | 0.2 | 0 | 0 | 0.4 | 0 | 0.7 | 0 | 0.2 |
| Qin 2020 | COVID 19 | ESR | approx SMD | *3.428571429* | *3.215686275* | *3.785714286* | 452 | 166 | 286 | 0.123 | *3.75* | *10.25* | *9* | *10.25* | *7.5* | 0 | 15 | 31.5 | 28 | 34 | 17 | 58 | 14 | 50 | 19 | 60 |
| Qin 2020 | COVID 19 | CRP | approx SMD | *4.415189873* | *4.982857143* | *5.512605042* | 452 | 166 | 286 | 0.001 | *0.25* | *19.5* | *12.875* | *20.575* | *0.5* | 0 | 1 | 44.1 | 33.2 | 57.9 | 15.5 | 93.5 | 8.2 | 59.7 | 20.9 | 103.2 |
| Qin 2020 | COVID 19 | TNF a | approx SMD | *3.008264463* | *3* | *2.952380952* | 452 | 166 | 286 | 0.037 | *2.025* | *1* | *0.875* | *1.125* | *4.05* | 0 | 8.1 | 8.6 | 8.4 | 8.7 | 6.9 | 10.9 | 6.9 | 10.4 | 7.1 | 11.6 |
| Qin 2020 | COVID 19 | IL-6 | approx SMD | *2.910602911* | *1.773755656* | *3.338461538* | 452 | 166 | 286 | 0.001 | *1.75* | *10.275* | *9.3* | *11.25* | *3.5* | 0 | 7 | 21 | 13.3 | 25.2 | 6.1 | 47.2 | 3.9 | 41.1 | 9.5 | 54.5 |
| Qin 2020 | COVID 19 | IL-8 | approx SMD | *-1.45177665* | *-1.867746289* | *-1.274336283* | 452 | 166 | 286 | 0.001 | *15.5* | *4.2* | *3.025* | *4.275* | *31* | 0 | 62 | 16.7 | 13.7 | 18.4 | 10.2 | 27 | 8.9 | 21 | 11.3 | 28.4 |
| Qin 2020 | COVID 19 | IL-10 | approx SMD | *0.492753623* | *0.324324324* | *1.064935065* | 452 | 166 | 286 | 0.001 | *2.275* | *1.175* | *0.5* | *1.575* | *4.55* | 0 | 9.1 | 5.4 | 5 | 6.6 | 5 | 9.7 | 5 | 7 | 5 | 11.3 |
| Qin 2020 | COVID 19 | NK cell activity | approx SMD | *-3.077354959* | *-2.831556503* | *-3.310701584* | 44 | 17 | 27 | 0.072 | *237.5* | *83.1* | *90.8* | *71.8* | *625* | 150 | 1100 | 131.7 | 160.2 | 113 |   |   |   |   |   |   |
| Qin 2020 | COVID 19 | Naïve Th cells | approx SMD | *-0.172727273* | *-0.76* | *0.223529412* | 44 | 17 | 27 | 0.035 | *6.5* | *13.3* | *13* | *12.2* | *42.41* | 29.41 | 55.41 | 40.7 | 35 | 44.5 |   |   |   |   |   |   |
| Qin 2020 | COVID 19 | Memory Th cells | approx SMD | *0.237837838* | *0.869019608* | *-0.129877217* | 44 | 17 | 27 | 0.035 | *6.125* | *13.3* | *13* | *12.2* | *56.69* | 44.44 | 68.94 | 59 | 65 | 55.5 |   |   |   |   |   |   |
| Raygan 2017 | Melatonin | CRP | SMD | *-1.64* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Alamdari 2014 | Melatonin | CRP | SMD | *0.22* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Pakravan 2015 | melatonin | CRP | SMD | *-2.81* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Javanmard 2016 | Melatonin | CRP | SMD | *-3.03* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Alamdari 2014 | Melatonin | IL-6 | SMD | *-3.54* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Celinski 2014 | Melatonin | IL-6 | SMD | *-1.99* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Cichoz-Lach 2010 | Melatonin | IL-6 | SMD | *-0.62* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Alamdari 2014 | Melatonin | TNF a | SMD | *-2.03* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Celinski 2014 | Melatonin | TNF a | SMD | *-3.58* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Cichoz-Lach 2010 | Melatonin | TNF a | SMD | *-0.06* |  |  |   |   |   |   | *0* | *0* | *0* | *0* | *0* |   |   |   |   |   |   |   |   |   |   |   |
| Dhanapalan 2020 | Remdesivir | CRP | approx SMD | *-3.481226627* | *0* | *0* | 48 | 38 |   | 0.001 | *44.9* | *21.95* | *0* | *0* | *161* | 71.2 | 250.8 | 44.64 |   |   | 28.2 | 116 |   |   |   |   |
| Dhanapalan 2020 | Remdesivir | CRP inside 48 hours | approx SMD | *-2.828046745* | *0* | *0* | 29 | 29 |   | 0.002 | *39.25* | *20.65* | *0* | *0* | *147.7* | 69.2 | 226.2 | 63 |   |   | 36.4 | 119 |   |   |   |   |
| Dhanapalan 2020 | Remdesivir | CRP after 48 hours | approx SMD | *-3.715178882* | *0* | *0* | 19 | 19 |   | 0.002 | *46.9* | *25.075* | *0* | *0* | *166.7* | 72.9 | 260.5 | 33 |   |   | 22.7 | 123 |   |   |   |   |
| Rausch-Fan 2002 | D3 | IL-6 (trans) | approx SMD | *-1.651685393* | *0* | *0* | 6 | 6 |   | 0.05 | *8.5* | *9.3* | *0* | *0* | *46.5* |   |   | 31.8 |   |   |   |   |   |   |   |   |
| Rausch-Fan 2002 | D3 | TNF a | approx SMD | *-2.64516129* | *0* | *0* | 6 | 6 |   | 0.005 | *2.2* | *0.9* | *0* | *0* | *7.7* |   |   | 3.6 |   |   |   |   |   |   |   |   |
| Bartels 2013 | D3 | TNF a | approx SMD | *-1.582644628* | *0* | *0* | 20 | 20 |   | 0.01 | *357* | *127* | *0* | *0* | *549* |   |   | 166 |   |   |   |   |   |   |   |   |
| Bartels 2013 | D3 | IL-10 | approx SMD | *-0.394618834* | *0* | *0* | 20 | 20 |   | 0.08 | *143* | *80* | *0* | *0* | *123* |   |   | 79 |   |   |   |   |   |   |   |   |
| Bartels 2013 | D3 | IL-6 classic | approx SMD | *0.772108844* | *0* | *0* | 20 | 20 |   | 0.01 | *1159* | *1781* | *0* | *0* | *1550* |   |   | 2685 |   |   |   |   |   |   |   |   |
| Smolen 2009 | Tocilizumab | CRP | 4mg approx SMD | *0.129032258* | *0* | *0* | 213 |   |   | 0.05 | *28* | *34* | *0* | *0* | *24* |   |   | 28 |   |   |   |   |   |   |   |   |
| Smolen 2009 | Tocilizumab | CRP | 8mg approx SMD | *0.074074074* | *0* | *0* | 205 |   |   | 0.05 | *28* | *26* | *0* | *0* | *24* |   |   | 26 |   |   |   |   |   |   |   |   |
| Smolen 2009 | Tocilizumab | ESR | 4mg approx SMD | *-0.018832392* | *0* | *0* | 213 |   |   | 0.05 | *26.3* | *26.8* | *0* | *0* | *49.7* |   |   | 49.2 |   |   |   |   |   |   |   |   |
| Smolen 2009 | Tocilizumab | ESR | 8mg approx SMD | *0.056710775* | *0* | *0* | 205 |   |   | 0.05 | *26.3* | *26.6* | *0* | *0* | *49.7* |   |   | 51.2 |   |   |   |   |   |   |   |   |
| Wang, Zhang 2020 | Remdesivir | Lymphocytes overall | approx SMD | *0.727272727* | *0* | *0* | 158 | 78 |   | na | *0.15* | *0.125* | *0* | *0* | *0.7* | 0.6 | 1.2 | 0.8 |   |   | 0.6 | 1.1 |   |   |   |   |
| Dhanapalan 2020 | Remdesivir | Ferritin | approx SMD | *0.010853975* | *0* | *0* | 48 |   |   |   | *294.75* | *350.175* | *0* | *0* | *1264.5* | 821 | 2000 | 1268 |   |   | 599.3 | 2000 |   |   |   |   |

*Table A7: Master reference guide for data used to determine standard means difference (SMD) or approximate standard mean difference (approx SMD). Ref = sourcing for extrapolated data, Catalyst = intervention or pathogen affecting marker, Target = inflammatory marker tracked, Delta Mech = the method by which change was determined, d1 = first group’s effect size (if only one group tracked, the primary effect size), d2 = second group’s effect size if present (test grouping can be found in relevant studies), d3 = third group’s effect size if present (test grouping can be found in relevant studies), n1 = first group’s sample size (if only one group tracked, the primary sample size), n2 = second group’s sample size if present (test grouping can be found in relevant studies), n3 = third group’s sample size if present (test grouping can be found in relevant studies), p = significance (where available), Control SD = standard deviation (listed or approximated) of control group, SD1 = standard deviation (listed or approximated) of first or primary group, SD2 = standard deviation (listed or approximated) of second group (test grouping can be found in relevant studies), SD3 = standard deviation (listed or approximated) of third group (test grouping can be found in relevant studies), Control x̅ = sample mean of the control (listed or approximated), CR Min = minimum range of values for control (if listed), CR Max = maximum range of values for control (if listed), x̅1 = sample mean first group (if only one group tracked, the primary sample mean), x̅2 = second group’s sample mean if present (test grouping can be found in relevant studies), x̅3 = third group’s sample mean if present (test grouping can be found in relevant studies), R1 Min = minimum range of values for group 1 (if only one group tracked, the primary sample minimum), R1 Max = maximum range of values for group 1 (if only one group tracked, the primary sample maximum), R2 Min = minimum range of values for group 2 (if listed), R2 Max = maximum range of values for group 2 (if listed), R3 Min = minimum range of values for group 3 (if listed), R3 Max = maximum range of values for group 3 (if listed).*

## Weighted mean difference conversion

Where effect sizes were reported, but formatted as weighted mean differences (WMD) rather than standard mean difference (SMD), conversions were performed to approximate the SMD effect sizes. Table A8 details the data that informed such conversions.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref | Catalyst | Target | Conversion | *d 1* | *WMD* | n | lower | upper | *SD* |
| Akbari 2020 | COVID 19 | CRP | wmd to smd approx | *2.567716667* | *41.07* | 37 | 29.76 | 52.38 | *15.99* |
| Akbari 2020 | COVID 19 | ESR | wmd to smd approx | *2.403957502* | *23.39* | 13 | 16.51 | 30.27 | *9.73* |
| Akbari 2020 | COVID 19 | Ferritin | wmd to smd approx | *2.691076914* | *594.25* | 8 | 438.1 | 750.4 | *220.8* |
| Akbari 2020 | COVID 19 | Lymphocytes overall | wmd to smd approx | *-4.141625433* | *-0.41* | 46 | -0.48 | -0.34 | *0.099* |
| Akbari 2020 | COVID 19 | Monocyte | wmd to smd approx | *-0.064282435* | *-0.04* | 18 | -0.89 | -0.01 | *0.622* |
| Akbari 2020 | COVID 19 | IL-2 | wmd to smd approx | *2.199887764* | *0.28* | 9 | 0.19 | 0.37 | *0.127* |
| Akbari 2020 | COVID 19 | IL-4 | wmd to smd approx | *0.96423652* | *0.15* | 10 | 0.04 | 0.26 | *0.156* |
| Akbari 2020 | COVID 19 | IL-6 trans | wmd to smd approx | *3.548499192* | *17.79* | 23 | 14.24 | 21.33 | *5.013* |
| Akbari 2020 | COVID 19 | IL-8 | wmd to smd approx | *0.89077088* | *5.82* | 4 | 1.2 | 10.44 | *6.534* |
| Akbari 2020 | COVID 19 | IL-10 | wmd to smd approx | *5.279730633* | *2.24* | 16 | 1.94 | 2.54 | *0.424* |
| Akbari 2020 | COVID 19 | TNF a | wmd to smd approx | *0.737850554* | *0.24* | 17 | 0.01 | 0.47 | *0.325* |
| Akbari 2020 | COVID 19 | INF-λ | wmd to smd approx | *1.46472119* | *0.58* | 11 | 0.3 | 0.86 | *0.396* |
| Akbari 2020 | COVID 19 | CD4 | wmd to smd approx | *-4.44222974* | *-218.34* | 21 | -253 | -184 | *49.15* |
| Akbari 2020 | COVID 19 | CD8 | wmd to smd approx | *-3.652707377* | *-148.23* | 21 | -177 | -120 | *40.58* |
| Akbari 2020 | COVID 19 | NK cell | wmd to smd approx | *-2.296653428* | *-43.75* | 14 | -57.2 | -30.3 | *19.05* |
| Akbari 2020 | COVID 19 | CD19 | wmd to smd approx | *-2.043025845* | *-33.27* | 15 | -44.8 | -21.8 | *16.28* |

Table A8: *Data used to approximate standard means difference (SMD) from weighted mean differences (WMD). Ref = sourcing for extrapolated data, Catalyst = intervention or pathogen affecting marker, Target = inflammatory marker tracked, Conversion = which values were converted into which format, d1 = primary group’s effect size, n = primary group’s sample size, Lower = lower range of wmd values, Upper = upper range of wmd values, SD = standard deviation for selected values*