# Face Masks as an Intervention to Reduce Aerosol and Droplet-based Transmission of Respiratory Infectious Disease:

# A Brief Assessment of the Science

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## Executive Summary

There is a lot of uncertainty about what the science behind face masks actually says. This is made more complicated by the fact that peer-reviewed, scientific literature is complex and is mostly intended to be read by other researchers and academics. Although the shift toward open access journals is gaining momentum, there are still thousands of peer-reviewed journals that are only available via purchase of a subscription. This current assessment is an attempt to briefly synthesize the scientific literature related to face masks.

**Note:** This document is not a full, systematic review of the literature. Systematic reviews (see below) usually take place over weeks or months and entail a number of researchers. This assessment was completed by one reader over the course of one week – and edited by a second health researcher – however, it represents the findings from a review of the most recent literature, pulled on 09/07/2021.

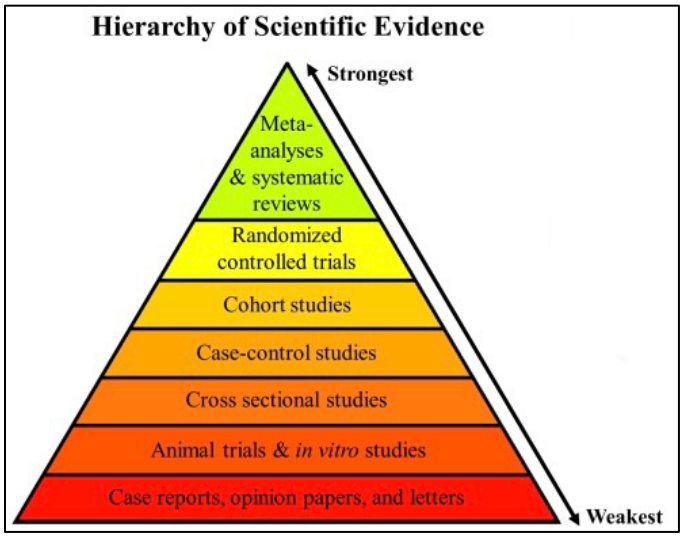
In the following pages, you will find summaries of the results of different studies related to the use of face masks to reduce transmission of COVID-19 and similar respiratory viruses. Before reviewing the various studies, it's important to understand the scientific process behind them and a few terms:

**Level of evidence:** There are millions of articles and studies that have been published in peer-reviewed journals. Just appearing in a journal does not mean that all evidence from any individual study is credible. Sometimes, studies will be published that show contrasting results. So, in science we look at the level of evidence – meaning we examine both how often a particular result or evidence is found and the quality of the research that produced the results. The *quality* of the research is also referred to as its *rigor*.

**Study design:** There are different types – or designs – of scientific studies. Sometimes a researcher watches and documents things that are happening or that have happened in the real world (*observational*). Other times, researchers work within a laboratory setting that, unlike the real world, can be highly controlled to look only at certain things (*experimental*). Some types of research involve writing a description of what is found (*qualitative*), while other types include numbers and statistical calculations associated with the findings (*quantitative*).

**Systematic Review and Meta-analysis:** A systematic review entails a rigorous and structured review of the literature on a particular topic, usually by more than one researcher. Systematic reviews follow protocols to ensure that they are reducing the level of bias in their findings as much as possible. If the studies included in the review involve statistical calculations, then the reviewers can also complete a meta-analysis. This adds power to the findings by increasing the total number of participants the results are found in. For example, if one study of 100 people found that 40 of them (40%) preferred winter over summer and another study of 400 people found 80 of them (20%) preferred winter over summer, the resulting total would be that 120 out of 500 people (24%) prefer winter over summer – the greater the number of people who are reported on in studies, the more confidence we have in our estimate.

**Hierarchy of evidence:** In order to help determine the level of evidence behind particular results, there is a hierarchy of evidence that ranks studies based on their level of rigor (see below). This is an attempt to get to the "best available evidence" – remember, just because one particular study generated a set of results does not mean those results are the most credible or rigorous evidence available.




**Hierarchy of scientific evidence**
Source: thelogicofscience.com

## How to read this assessment

While still limited, there are several peer-reviewed systematic reviews and meta-analyses examining the topic of face masks and respiratory illness. These reviews are included first, and they cover a combined total of more than **30,000 study participants** as well as observations from large communities around the globe. We also found two studies that focus specifically on children. As COVID-19 is a newly emerging research topic, we only included articles published in 2020 or 2021.

Each summary includes the title of the article, year it was published, type of study, and results. For some of the articles that were published in open-access journals, we also included a graphic from the studies. These graphics can be found immediately below the summary to which they apply.

## Table of Contents

## STUDIES EXAMINING BENEFITS OF MASKING

**1. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis[1]**
**Journal:** European Journal of Medical Research
**Year:** 2021
**Design:** Systematic Review and Meta-analysis
**Results:** The analysis included four articles with a combined sample size of 7,688 participants. The result of this meta-analysis has shown a significant reduction in risk of SARS-CoV-2 infection with face mask use. When pooling the results from the four studies, **there was an estimated 88% decrease in risk** (95% CI: 73% - 94% decreased risk) of COVID-19 infection among face mask users as compared to non-users.

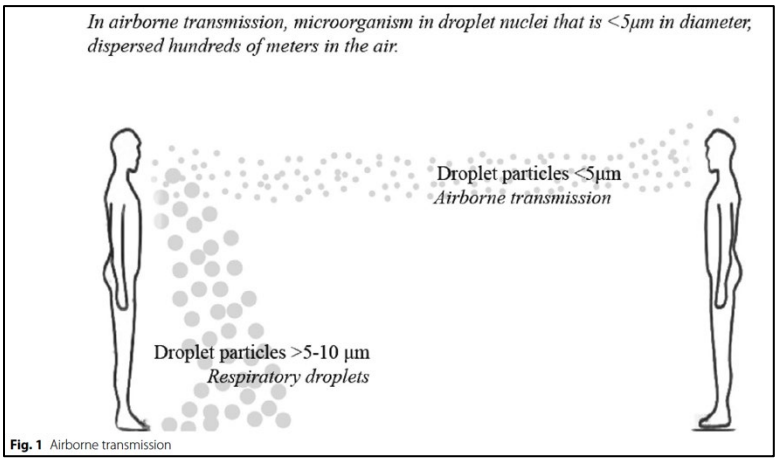


**Fig. 1** Airborne transmission

**2. Face masks to prevent transmission of COVID-19: A systematic review and meta-analysis[2]**
**Journal:** American Journal of Infection Control
**Year:** 2021
**Design:** Systematic Review and Meta-analysis
**Results:** The analysis included six articles with a combined sample size of 1,233 participants. The quality of the studies was mostly high (n = 5), with one study of fair quality. The **combined results showed 62% lower odds** (95% CI: 31% - 79% lower odds) of COVID-19 infection among individuals wearing masks as compared to those not wearing masks.

**3. Face Mask Use in the Community for Reducing the Spread of COVID-19: A Systematic Review[3]**
**Journal:** Frontiers in Medicine
**Year:** 2021
**Design:** Systematic Review and Meta-analysis
**Results:** The review included 35 articles - three were cluster randomized control trials, two were cohort studies, four were case-control studies, four were cross-sectional studies, 13 were quantitative-deterministic predictive models, and nine were experimental studies. Seven of the studies looked specifically at COVID-19, while others looked at influenza, H1N1 influenza, SARS, or similar respiratory infections. The quality of individual studies ranged from poor to fair, which translates to low certainty of the evidence. However, within the findings there is weak evidence that masks, regardless of type, work to reduce viral transmission. Finally, **no studies reported** an increase in transmission rates due to masking.

**4. Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis[4]**
**Journal:** Travel Medicine and Infectious Disease
**Year:** 2020
**Design:** Systematic Review and Meta-analysis
**Results:** The review and analysis included 21 articles, with a combined sample size of 8,686 participants. The quality of the case-control and cohort studies (n = 15) was mostly high (n = 13), with two studies of fair quality. The **pooled results demonstrated 65% reduced odds** (95% CI: 49% - 76% reduced odds) of contracting a viral infection after wearing a mask.

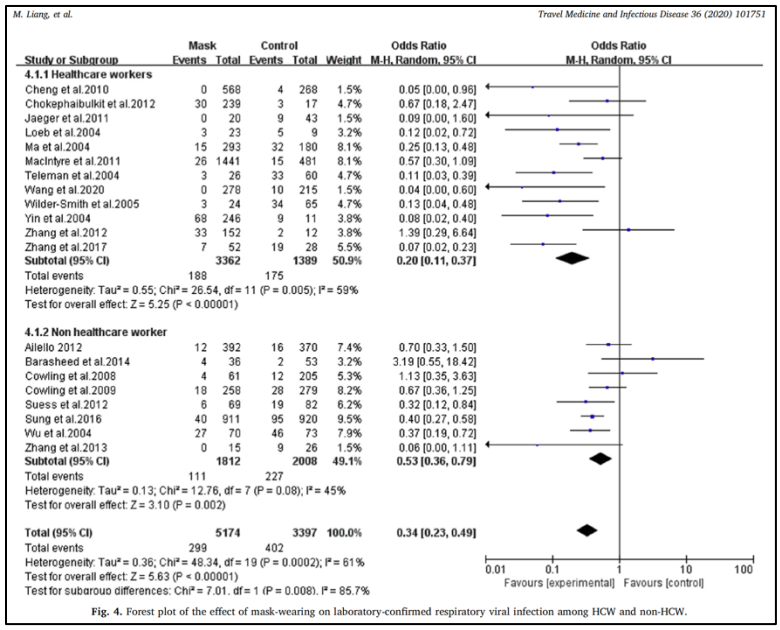
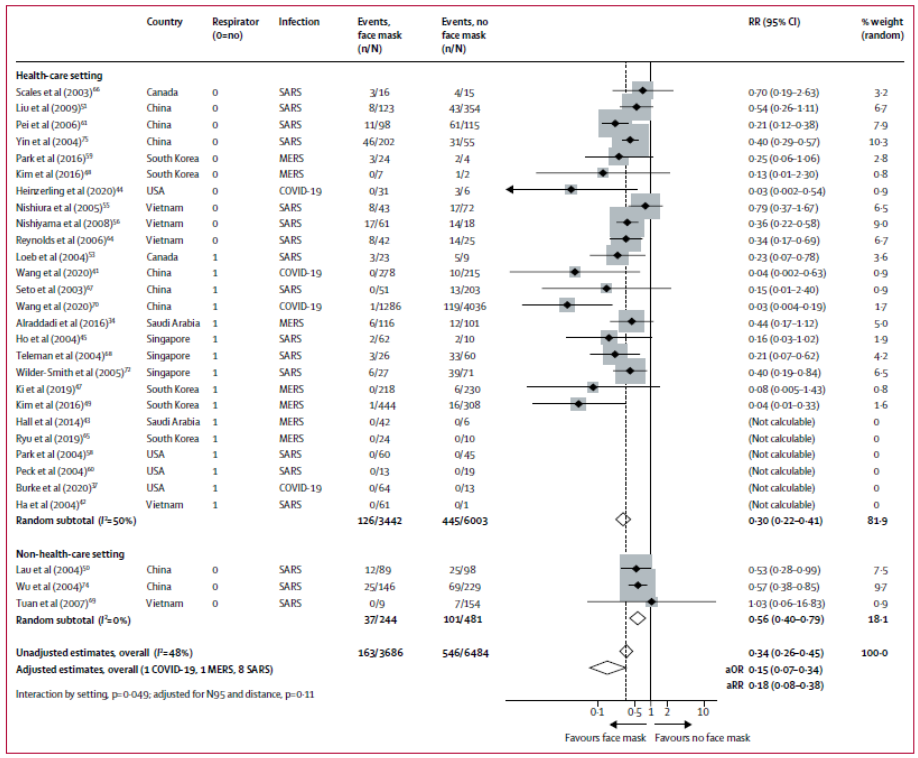


**Fig. 4.** Forest plot of the effect of mask-wearing on laboratory-confirmed respiratory viral infection among HCW and non-HCW.

**5. Face Masks and the Cardiorespiratory Response to Physical Activity in Health and Disease[5]**
**Journal:** Annals of the American Thoracic Society
**Year:** 2021
**Design:** Focused Review
**Results:** The researchers found that face masks may be associated with increased rates of dyspnea (a subjective, self-reported experience of breathing discomfort), but did not find any concerning results in published studies that explore work of breathing (Wb), arterial blood gasses, muscle blood flow, cerebral blood flow, and dyspnea. The researchers further examined findings based on subpopulations of older adults, pediatrics, sex-based differences, and patients with cardiopulmonary disease. While small, difficult-to-detect physiological effects can occur with mask use, the **researchers found no evidence to suggest any specific dangers** associated with wearing face masks while exercising.

**6. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis[6]**
**Journal:** Lancet
**Year:** 2020
**Design:** Systematic Review and Meta-analysis
**Results:** The review included 172 studies in both healthcare and non-healthcare settings that examined COVID-19, SARS, and MERS infection. The portion of the analysis that focused on face masks included a combined sample size of 12,817 participants. The anticipated chance of infection/transmission for those

in the face mask group was **an average of 14.3% lower** than for no mask, with N95 masks showing the greatest reduction in transmission. **No studies reported** an increase in transmission risk associated with mask use.



| | Country | Respirator (0=no) | Infection | Events, face mask (n/N) | Events, no face mask (n/N) | RR (95% CI) | % weight (random) |
|---|---|---|---|---|---|---|---|
| **Health-care setting** | | | | | | | |
| Scales et al (2003)[66] | Canada | 0 | SARS | 3/16 | 4/15 | 0·70 (0·19–2·63) | 3·2 |
| Liu et al (2009)[53] | China | 0 | SARS | 8/123 | 43/354 | 0·54 (0·26–1·11) | 6·7 |
| Pei et al (2006)[42] | China | 0 | SARS | 11/98 | 61/115 | 0·21 (0·12–0·38) | 7·9 |
| Yin et al (2004)[75] | China | 0 | SARS | 46/202 | 31/55 | 0·40 (0·29–0·57) | 10·3 |
| Park et al (2016)[59] | South Korea | 0 | MERS | 3/24 | 2/4 | 0·25 (0·06–1·06) | 2·8 |
| Kim et al (2016)[69] | South Korea | 0 | MERS | 0/7 | 1/2 | 0·13 (0·01–2·30) | 0·8 |
| Heinzerling et al (2020)[44] | USA | 0 | COVID-19 | 0/31 | 3/6 | 0·03 (0·002–0·54) | 0·9 |
| Nishiura et al (2005)[55] | Vietnam | 0 | SARS | 8/43 | 17/72 | 0·79 (0·37–1·67) | 6·5 |
| Nishiyama et al (2008)[56] | Vietnam | 0 | SARS | 17/61 | 14/18 | 0·36 (0·22–0·58) | 9·0 |
| Reynolds et al (2006)[64] | Vietnam | 0 | SARS | 8/42 | 14/25 | 0·34 (0·17–0·69) | 6·7 |
| Loeb et al (2004)[53] | Canada | 1 | SARS | 3/23 | 5/9 | 0·23 (0·07–0·78) | 3·6 |
| Wang et al (2020)[45] | China | 1 | COVID-19 | 0/278 | 10/215 | 0·04 (0·002–0·63) | 0·9 |
| Seto et al (2003)[67] | China | 1 | SARS | 0/51 | 13/203 | 0·15 (0·01–2·40) | 0·9 |
| Wang et al (2020)[70] | China | 1 | COVID-19 | 1/1286 | 119/4036 | 0·03 (0·004–0·19) | 1·7 |
| Alraddadi et al (2016)[34] | Saudi Arabia | 1 | MERS | 6/116 | 12/101 | 0·44 (0·17–1·12) | 5·0 |
| Ho et al (2004)[45] | Singapore | 1 | SARS | 2/62 | 2/10 | 0·16 (0·03–1·02) | 1·9 |
| Teleman et al (2004)[68] | Singapore | 1 | SARS | 3/26 | 33/60 | 0·21 (0·07–0·62) | 4·2 |
| Wilder-Smith et al (2005)[72] | Singapore | 1 | SARS | 6/27 | 39/71 | 0·40 (0·19–0·84) | 6·5 |
| Ki et al (2019)[47] | South Korea | 1 | MERS | 0/218 | 6/230 | 0·08 (0·005–1·43) | 0·8 |
| Kim et al (2016)[69] | South Korea | 1 | MERS | 1/444 | 16/308 | 0·04 (0·01–0·33) | 1·6 |
| Hall et al (2014)[61] | Saudi Arabia | 1 | MERS | 0/42 | 0/6 | (Not calculable) | 0 |
| Ryu et al (2019)[65] | South Korea | 1 | MERS | 0/24 | 0/10 | (Not calculable) | 0 |
| Park et al (2004)[58] | USA | 1 | SARS | 0/60 | 0/45 | (Not calculable) | 0 |
| Peck et al (2004)[60] | USA | 1 | SARS | 0/13 | 0/19 | (Not calculable) | 0 |
| Burke et al (2020)[37] | USA | 1 | COVID-19 | 0/64 | 0/13 | (Not calculable) | 0 |
| Ha et al (2004)[62] | Vietnam | 1 | SARS | 0/61 | 0/1 | (Not calculable) | 0 |
| **Random subtotal ($I^2$=50%)** | | | | **126/3442** | **445/6003** | **0·30 (0·22–0·41)** | **81·9** |
| **Non-health-care setting** | | | | | | | |
| Lau et al (2004)[50] | China | 0 | SARS | 12/89 | 25/98 | 0·53 (0·28–0·99) | 7·5 |
| Wu et al (2004)[74] | China | 0 | SARS | 25/146 | 69/229 | 0·57 (0·38–0·85) | 9·7 |
| Tuan et al (2007)[69] | Vietnam | 0 | SARS | 0/9 | 7/154 | 1·03 (0·06–16·83) | 0·9 |
| **Random subtotal ($I^2$=0%)** | | | | **37/244** | **101/481** | **0·56 (0·40–0·79)** | **18·1** |
| **Unadjusted estimates, overall ($I^2$=48%)** | | | | **163/3686** | **546/6484** | **0·34 (0·26–0·45)** | **100·0** |
| **Adjusted estimates, overall (1 COVID-19, 1 MERS, 8 SARS)** | | | | | | **aOR 0·15 (0·07–0·34)** | |
| | | | | | | **aRR 0·18 (0·08–0·38)** | |

Interaction by setting, p=0·049; adjusted for N95 and distance, p=0·11



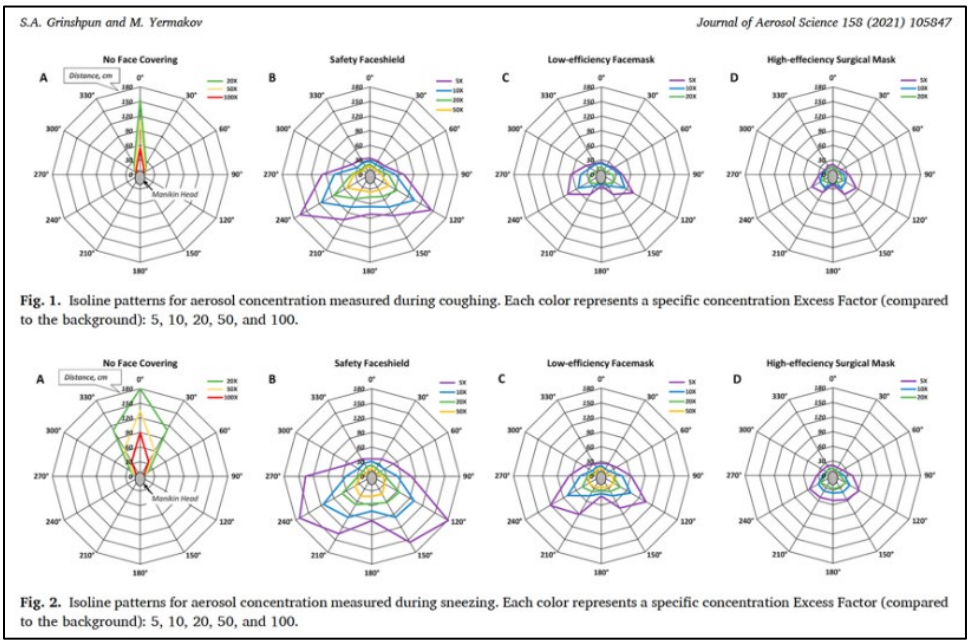
*Figure 4:* **Forest plot showing unadjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS**
SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

**7. Face masks, public policies and slowing the spread of COVID-19: Evidence from Canada[7]**
**Journal:** Journal of Health Economics
**Year:** 2021
**Design:** Ecological Study
**Results:** Researchers were able to study the association between staggered mask mandates among Canadian provinces on the incidence rates of COVID-19. Controlling for mobility behavior and lagged case totals, they **found a 22% weekly reduction in COVID-19 incidence** associated with mask mandates. They also found that the mask mandates increased self-reported mask wearing in public by about 27 percentage points. Their results support face masks as a mitigation intervention against COVID.

**8. Data-driven estimation of change points reveals correlation between face mask use and accelerated curtailing of the first wave of the COVID-19 epidemic in Italy[8]**
**Journal:** Infectious Diseases
**Year:** 2021
**Design:** Ecological Study
**Results:** Researchers were able to study the association between regional interventions on the incidence rates of COVID-19. Controlling for a number of factors, including testing rates, lagged case totals, mobility data, and weather patterns, and were able to identify change points (significant changes in the incidence rate) that **correlate with both lockdown and regional mask mandates** and/or large-scale distributions of free face masks. **Their results support the use of face masks** for controlling the spread of COVID-19.

**9. A rapid review of the use of face mask in preventing the spread of COVID-19[9]**
**Journal:** International Journal of Nursing Studies Advances
**Year:** 2021
**Design:** Rapid Review
**Results:** The review included 58 studies, of which 13 were systematic reviews and 45 were quantitative studies. All of the studies that compared mask use to non-use found **higher rates of respiratory virus transmission among the non-use participants**. Effectiveness of mask use in preventing illness ranged from no benefit (n = 7) to significant benefit (n = 19). The majority (n = 32) of studies showed some evidence of potential benefit and **no studies showed** an increase in COVID transmission associated with mask use. Of the five studies that examined mask use and hand hygiene combined, three showed significantly lower levels of transmission.

**10. Technical note: Impact of face covering on aerosol transport patterns during coughing and sneezing[10]**
**Journal:** Journal of Aerosol Science
**Year:** 2021
**Design:** Laboratory experiment
**Results:** This study focused on sub-micrometer aerosol particles. Three different types of masks were tested in a laboratory setting, along with no mask. When no mask was worn, aerosol particles up to six feet in forward distance were highly elevated (up to 20x normal concentration) both while coughing or sneezing. A safety face shield delivered protection forward, but rear spread still reached up to 5x normal concentration. The low efficiency facemask reduced spread considerably compared to the face shield, but the **high efficiency mask made the greatest impact** on reducing spread.



## STUDIES EXAMINING EFFECTS OF MASKING IN CHILDREN

**1. A randomised clinical trial to evaluate the safety, fit, comfort of a novel N95 mask in children[11]**
**Journal:** Scientific Reports
**Year:** 2019
**Design:** Randomized crossover experiment
**Results:** 106 children (ages 7 to 14 years) participated. Outcome measures included end-tidal carbon dioxide ($ETCO_2$), fractional inspired carbon dioxide ($FICO_2$), respiratory rate (RR), heart rate (HR), and oxygen saturation ($SpO_2$). Children participated in reading and brisk treadmill walking both with and without N95 masks. During all activities, the **physiological parameters for all children remained within the acceptable range**. Seven percent of the children (4 males and 3 female subjects) subjectively indicated that they experienced mild breathing difficulty, while 93% of the children experienced no breathing difficulty when using a mask. However, physiological measurements of the seven children who reported mild breathing difficulty were minimally different those children who did not.

| | Without mask (Control) | | With mask only (A) | | With mask and with micro fan (B) | |
|---|---|---|---|---|---|---|
| **Physiological parameters** | **7 subjects** | **99 subjects** | **7 subjects** | **99 subjects** | **7 subjects** | **99 subjects** |
| **Mean (SD) $ETCO_2$, mmHg** | | | | | | |
| At rest (Reading) | 29.1 (2.89) | 30.9(3.4) | 32.9 (3.18) | 34.3 (3.3) | 30.1 (4.16) | 32.2 (3.3) |
| On mild exertion (Brisk walking on treadmill) | 27.1 (2.02) | 28.2 (2.8) | 31.2 (1.61) | 32.0(2.8) | 29.8 (1.27) | 30.6 (3.1) |
| **Mean (SD) $FICO_2$, mmHg** | | | | | | |
| At rest (Reading) | 7.9 (2.11) | 8.2 (1.9) | 9.8 (2.58) | 10.7 (2.6) | 7.7 (1.52) | 7.8 (2.1) |
| On mild exertion (Brisk walking on treadmill) | 9.4 (1.46) | 9.9 (1.7) | 11.7 (2.05) | 12.1 (2.5) | 10.6 (2.41) | 10.8 (2.3) |
| **Mean (SD) RR, bpm** | | | | | | |
| At rest (Reading) | 17.6 (3.15) | 18.0 (3.2) | 16.7 (3.67) | 17.4 (3.6) | 16.2 (3.47) | 16.8 (3.3) |
| On mild exertion (Brisk walking on treadmill) | 23.4(2.79) | 23.5 (3.5) | 23.5 (4.28) | 23.2 (3.7) | 23.4 (4.04) | 23.2 (3.9) |
| **Mean (SD) HR /bpm** | | | | | | |
| At rest (Reading) | 91.8 (10.67) | 89.6 (11.3) | 92.3(11.91) | 90.7 (11.4) | 91.1(12.77) | 89.2 (11.3) |
| On mild exertion (Brisk walking on treadmill) | 108.7(11.66) | 108.4 (9.8) | 109.4(9.82) | 110.2 (7.7) | 110.5(7.63) | 109.5 (7.8) |
| **Mean (SD) $SpO_2$/%** | | | | | | |
| At rest (Reading) | 99.1 (0.75) | 99.6 (0.5) | 99.0 (0.77) | 99.5 (0.5) | 99.1 (0.77) | 99.6 (0.5) |
| On mild exertion (Brisk walking on treadmill) | 99.0 (0.61) | 99.2 (0.8) | 99.1 (0.45) | 99.2 (0.6) | 99.1 (0.49) | 99.2 (0.8) |

**Table 2.** Comparison of the mean $ETCO_2$, $FICO_2$ and other physiological parameters for subjects indicating experiencing mild breathing difficulty on VAS (7) vs the rest of the participants (99). $ETCO_2$ = end-tidal carbon dioxide, $FICO_2$ = fractional inspired carbon dioxide, RR = respiratory rate, $SpO_2$ = oxygen saturation, HR = Heart rate.

**2. Assessment of the Wearability of Facemasks against Air Pollution in Primary School-Aged Children in London[12]**
**Journal:** International Journal of Environmental Research and Public Health
**Year:** 2020
**Design:** Pilot Study
**Results:** 24 children (ages 8 to 11 years) participated. They wore three different kinds of face masks (one each day for three days in a row) that were not clinically fitted and completed three minutes of gentle walking followed by three minutes of running while wearing the masks. The researchers then asked the children about: (1) comfort; (2) hotness; (3) breathability; (4) fit; (5) embarrassment; and (6) aesthetics. The main complaint was hotness while running. The mask the children liked most (highest ratings in fit, embarrassment, and appearance, and most likely to wear again) was the cloth mask with micro ventilator, even though they rated the disposable masks as easier to breathe through. This may indicate an impact of social desirability on the subjective measures of breathability and embarrassment. All 24 children completed the study in full and **no children needed to withdraw due to any physiological concerns**.

## STUDIES EXAMINING DETRIMENTAL EFFECTS OF MASKING

**1. Downsides of face masks and possible mitigation strategies: a systematic review and meta-analysis[13]**
**Journal:** BMJ Open
**Year:** 2021
**Design:** Systematic Review and Meta-analysis
**Results:** The review included 37 studies (40 articles). Four studies, with a combined study sample of 93 participants, noted minor physiological effects. For the most part, these included subjective reports of increased difficulty in breathing, along with reduced nasal spirometry (increased breathing through the mouth) and subjective reports of increased breathing resistance. **No major physiological effects of concern were identified**. The greatest detrimental effect noted was increased difficulty in communication, almost entirely in healthcare settings. Overall, studies favored face masks. Greater compliance was associated with surgical masks over N95 masks, and **the authors report insufficient data to quantify adverse effects** and note that more research is needed.

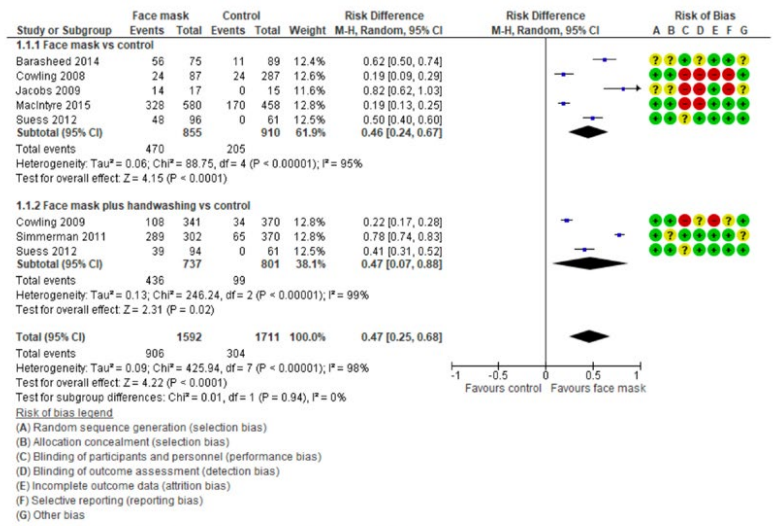


**Figure 3** Comparison of adherence to face masks versus control.

**Articles that claimed masks are ineffective or detrimental but were later retracted due to concerns with the science:**


Bae S, Kim MC, Kim JY, et al. Effectiveness of surgical and cotton masks in blocking SARS-CoV-2: a controlled comparison in 4 patients. *Ann Intern Med*. 2020;173(1):W22-W23.

Vainshelboim B. Facemasks in the COVID-19 era: A health hypothesis. *Med Hypotheses*. 2021; 146.

Walach H, Weikl R, Prentice J, Diemer A, Traindl H, Kappes A, Hockertz S. Experimental Assessment of Carbon Dioxide Content in Inhaled Air With or Without Face Masks in Healthy Children: A Randomized Clinical Trial. *JAMA Pediatrics*. 2021. doi:10.1001/jamapediatrics.2021.2659.

References


1. Tabatabaeizadeh S-A. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. *EUR J MED RES.* 2021;26(1):1-1.
2. Li Y, Liang M, Gao L, et al. Face masks to prevent transmission of COVID-19: A systematic review and meta-analysis. *Am J Infect Control.* 2021;49(7):900-906.
3. Coclite D, Napoletano A, Gianola S, et al. Face Mask Use in the Community for Reducing the Spread of COVID-19: A Systematic Review. *FRONT MED-LAUSANNE.* 2021;7:594269-594269.
4. Liang M, Gao L, Cheng C, et al. Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis. *TRAVEL MED INFECT DI.* 2020;36:101751-101751.
5. Hopkins SR, Dominelli PB, Davis CK, et al. Face Masks and the Cardiorespiratory Response to Physical Activity in Health and Disease. *Ann Am Thorac Soc.* 2021;18(3).
6. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *LANCET.* 2020;395(10242):1973-1987.
7. Karaivanov A, Lu SE, Shigeoka H, Chen C, Pamplona S. Face masks, public policies and slowing the spread of COVID-19: Evidence from Canada. *Journal of health economics.* 2021;78:102475-102475.
8. Pedersen MG, Meneghini M. Data-driven estimation of change points reveals correlation between face mask use and accelerated curtailing of the first wave of the COVID-19 epidemic in Italy. *INFECT DIS-NOR.* 2021;53(4):243-251.
9. Abboah-Offei M, Salifu Y, Adewale B, Bayuo J, Ofosu-Poku R, Opare-Lokko EBA. A rapid review of the use of face mask in preventing the spread of COVID-19. *Int J Nurs Stud Adv.* 2021;3:100013-100013.
10. Grinshpun SA, Yermakov M. Technical note: Impact of face covering on aerosol transport patterns during coughing and sneezing. *Journal of aerosol science.* 2021;158:105847-105847.
11. Goh DYT, Mun MW, Lee WLJ, Teoh OH, Rajgor DD. A randomised clinical trial to evaluate the safety, fit, comfort of a novel N95 mask in children. *SCI REP-UK.* 2019;9(1):18952-18910.
12. Smart NR, Horwell CJ, Smart TS, Galea KS. Assessment of the Wearability of Facemasks against Air Pollution in Primary School-Aged Children in London. *INT J ENV RES PUB HE.* 2020;17(11):3935.
13. Bakhit M, Krzyzaniak N, Scott AM, Clark J, Glasziou P, Del Mar C. Downsides of face masks and possible mitigation strategies: a systematic review and meta-analysis. *BMJ OPEN.* 2021;11(2):e044364.