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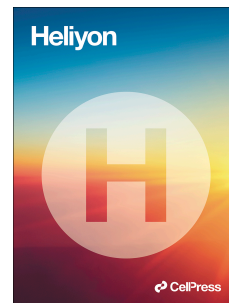
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# Possible toxicity of chronic carbon dioxide exposure associated with face mask use, particularly in pregnant women, children and adolescents – a scoping review

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## Abstract

*Introduction:* During the SARS-CoV2-pandemic, face masks have become one of the most important ubiquitous factors affecting human breathing. It increases the resistance and dead space volume leading to a re-breathing of CO<sub>2</sub>. So far, this phenomenon and possible implications on early life has not been evaluated in depth.

*Method:* As part of a scoping review, literature was systematically reviewed regarding CO<sub>2</sub> exposure and facemask use.

*Results:* Fresh air has around 0.04% CO<sub>2</sub>, while wearing masks more than 5 minutes bears a possible chronic exposure to carbon dioxide of 1.41% to 3.2% of the inhaled air. Although the buildup is usually within the short-term exposure limits, long-term exceedances and consequences must be considered due to experimental data. US Navy toxicity experts set the exposure limits for submarines carrying a female crew to 0.8% CO<sub>2</sub> based on animal studies which indicated an increased risk for stillbirths. Additionally, mammals who were chronically exposed to 0.3% CO<sub>2</sub> the experimental data demonstrate a teratogenicity with irreversible neuron damage in the offspring, reduced spatial learning caused by brainstem neuron apoptosis and reduced circulating levels of the insulin-like growth factor-1. With significant impact on three readout parameters (morphological, functional, marker) this chronic 0.3% CO<sub>2</sub> exposure has to be defined as being toxic. Additional data exists on the exposure of chronic 0.3% CO<sub>2</sub> in adolescent mammals causing neuron destruction, which includes less activity, increased anxiety and impaired learning and memory. There is also data indicating testicular toxicity in adolescents at CO<sub>2</sub> inhalation concentrations above 0.5%.

*Discussion:* There is a possible negative impact risk by imposing extended mask mandates especially for vulnerable subgroups. Circumstantial evidence exists that extended mask use may be related to current observations of stillbirths and to reduced verbal motor and overall cognitive performance in children born during the pandemic. A need exists to reconsider mask mandates.

## 1. Introduction

Approximately 77% of the countries in the world introduced the requirement to wear masks in public spaces to contain SARS-CoV-2 making it commonplace in 2020 [1]. Simultaneously, it is one of the most important ubiquitous environmental factors directly affecting human breathing. Government data from the end of the year 2021 show that an estimated 4 496 149 755 people worldwide (58% of world population) have been confronted with a mask obligation [1]. Given this and the significant role masks have played as a non-occupational, non-pharmaceutical public health intervention for the past 2 years, a rigorous scientific toxicological consideration is required. In many countries around the world children in schools in particular are/have been heavily exposed to the mandatory wearing of masks for long periods [2–6]. In this paper, we highlight the toxicological aspects of wearing a mask for special user groups resulting from a low-level CO<sub>2</sub> exposure.

In medical facilities and environments, where preventive measures against infections must be taken (e.g. operating room, isolation rooms due to confirmed infections etc.), masks have been considered an important self-protective and third-party protective equipment for healthcare workers prior to COVID-19 [7,8]. Laboratory tests on humans have demonstrated the efficacy of this medical device in reducing transmission of pathogens, especially bacteria [9]. Nevertheless, the effectiveness of masks in health care settings was debatable even before 2020 [10]. Since decades national and international standards for bacteria filtration efficiency (BFE) exist for medical masks, e.g. the EU-EN 14683, or the USA-ASTM F2101, and they are the prerequisites for general approval. However, no comparable standard/testing of masks for viruses has been established (not required by the FDA nor standardized by ASTM). In an important human subject evaluation with NaCl aerosol representing bacterial and viral particle size range, the general filtration efficacy of surgical and N95

masks (protection factor) for bigger, bacteria sized particles (0.5–5.0 micrometers in diameter) was better [9]. Interestingly, most of the tested N95 respirators and surgical masks performed at their worst against particles approximately between 0.04 and 0.2  $\mu\text{m}$ , which includes the sizes of Coronavirus and Influenza virus [9]. Indeed, some modelling and in vitro laboratory simulation studies (artificial conditions) aim to demonstrate less virus transmission when masks are used [11–13]. However, they have pitfalls, e.g. by only mathematically estimating the effect of mask wearing on transmission (no direct measurement of the effect by the observer himself, use of external data from a Facebook survey to derive mask wearing without in-depth quality assessment of wearing data, estimates of mask wearing) [11]. Accordingly, the authors of the study point out that unobserved factors can influence R [11]. Furthermore, the analysis window in that study was limited to the period from May to September, which is known to be the season with the lowest virus infection rates. On top of that, the calculated relative average transmission reduction of 19% is rather low. Other studies which claim that surgical masks are effective at preventing virus spread for example present calculations with statistical uncertainties, which make the relevance of statements derived from them close to zero: Due to standard deviations, they lie between 40% and 100% (Wuhan, Singapore, Gainesville and Omaha), in the worst case even between 10% and 100% (Hong Kong) [12]. The efficiency of the masks postulated is non-linearly dependent on the viral load in the breathing air. Moreover, calculations are based on a postulate with a mean infection probability between 0.8% and 4.0%. Thus, a wide range of  $P_{\text{inf}}$ -values (1%-100%) is noted [12]. The modelling of the aerosol particle penetration ( $<100\mu\text{m}$ ) has serious shortcomings. As demonstrated in supplementary figure S10 of the study in discussion which considers data from other experimental works the retention/penetration values for mask for particles at 0.125  $\mu\text{m}$  diameter range from 20 up to 80%, exhibiting a large deviation [12]. And naked viroids of less than one micrometer in diameter (e.g. 0.06-0.12 $\mu\text{m}$  for coronaviruses) are not comparable to other heavier particles of the same size. According to experimental studies, masks act like nebulizers and produce finer aerosols in percentage terms. An

ejection of a 60% fraction of particles with 0.3-0.5 $\mu$ m when breathing through N95, 46% with surgical and only 35% without mask has been measured [14]. Such smaller particles fly further and also float around the room longer than the larger aerosol particles released by people without masks [14]. This is due to rapid gravitational settling, respiratory droplets larger than 100  $\mu$ m are removed from the air in seconds [12] while smaller particles remain in the air longer. In addition, there is the empirically proven viral contamination of masks [15]. These higher proportions of potentially fine virus-containing aerosols in the air are not considered in the calculations (inhaled virus number factor in formula of the publication in discussion ) [12]. Another pitfall of studies, which try to prove the efficacy of face masks are artificial laboratory conditions with a simulation character that is not equivalent to the real world [13] and with no ecological validity (generalizability of experimental results to the real world, e.g., to situations or environments typical of daily life). In the experiments mentioned, the edges of the masks were sealed with adhesive tape. However, medical masks (surgical masks and even N95 masks) were not able to block the transmission of virus droplets/aerosols even when completely sealed [13]. But in real life scenarios, there are many problems of application errors/material defects that reduce such modelled or assumed protective mask efficiency. For example, if leakage (material defect, adaptation to face) is 1% of the mask, the efficiency is reduced by 50%, if the gap/hole is 2% of the mask, the efficiency is reduced by 75% [16]. Moreover, the apparent exhalation filtration efficiency has been shown to be significantly lower than the ideal (theoretical) filtration efficiency of the mask material (12.4% and 46.3% for surgical and N95 masks, respectively) [17]. Thus, the modelling and the desired antiviral face mask effect, from an empirical point of view, is far from reality.

The use of face masks belongs in the hands and under the supervision of medical professionals [18]. It is widely believed that the use of masks – including in the general population – could be an important measure to combat SARS-CoV2 [19]. Yet empirical scientific evidence for the moderate or

strong effectiveness of masks when used by the general population is lacking even in the Cochrane database [20,21] which analyses systematic reviews [22,23] and overviews of reviews [24]. The basis for the evaluation of any medical intervention is randomised clinical trials (RCTs): "Clinical experience or observational studies should never be used as the sole basis for evaluating the effects of an intervention - randomised clinical trials (RCTs) are always required" [25,26]. At the time of writing, 16 RCTs evaluating the efficacy of masks in preventing respiratory virus transmission compared with controls (no mask) have been available in the scientific literature [27–42] and only 2/16 (12.5%) clinical trials showed a statistically significant benefit of masks [30,42]. Lack of efficacy was demonstrated in 8/8 (100%) RCTs evaluating the effect of masks in the home setting, in 4/5 (80%) RCTs on the efficacy of wearing masks in the community and in 1/1 (100%) RCTs involving healthcare settings. Among the available RCTs on the antiviral efficacy of masks, only two clinical trials deal exclusively with COVID-19: one methodically sound study from Denmark Europe, showing no significant effect of masks [41], and the other from Bangladesh that supports mask efficiency [42]. The latter study included unblinded participants to self-report symptoms before testing, used an antibody test with a very low sensitivity, and exhibited unclear generalization from the specific context. The antibody detection was performed using a single commercial FDA emergency-use-authorized (EUA) serology test that is not suitable for the intended application to SARS-CoV-2 in Bangladesh (not calibrated or validated for populations in Bangladesh with undetermined cross-reactivity against broad-array IgM antibodies, malaria, influenza, etc.). The participants (individual level, family level, village level) in the control and treatment arms were systematically handled in palpably different ways that are linked to factors established to be strongly associated to infection and severity with viral respiratory diseases, in particular, and to individual health in general. In addition, the confidence interval of the relative risk (RR) contained the 1, corresponding to no effect [42,43]. Moreover, current evidence suggests that SARS-CoV-2 may be also transmitted via faecal and fomite transmission [44] between infected individuals and others.

Seeing the overall weak evidence for the efficacy of masks against viral transmission within the general population, from a purely evidence-based empirical perspective, masks for the public seem to be overrated in a pandemic response [20–24,45–47]. There is discrepancy between the evaluation of virus protection by face mask based in evidence-based criteria (low) and the anticipated efficacy by authorities and mainstream media (high).

In contrast, it is known that masks bear several side effects and risks [48]. There is a high risk of improper handling when the mask is used by the general population and by children [49,50]. A lack of correlation between school mask mandates and paediatric COVID-19 cases could recently be shown in a vast study which replicated the CDC study [51] and extended it to more districts and for a longer period, employing seven times as much data (November 30, 2021 instead of September 4, 2021, and 1812 counties instead 565 counties). The association between school mask mandates and cases did not persist in the extended sample [52]. Other researchers found no significant differences in SARS-CoV-2 transmission due to face mask mandates in Catalanian schools. Instead, age was the most important factor in explaining the transmission risk for children attending school [46]. Children and pregnant women are a special subgroup more susceptible to potential negative environmental factors (e.g. toxins) because the protective/conjugative mechanisms in early life tissues are less well developed [53]. Data on a total of 25,930 children wearing face masks for 270 min per day showed that 68% complained about impairments. Side effects included irritability (60%), headache (53%), difficulty concentrating (50%), less happiness (49%), reluctance to go to school/kindergarten (44%), malaise (42%) impaired learning (38%) and drowsiness/fatigue (37%) [4]. In addition, in another 6-minute experimental study, the masks frequently led to breathing problems in 100 school children between 8 and 11 years of age especially during physical exertion [54]. Despite having the lowest risk of severe disease from a SARS-CoV-2 infection, children have endured the most disproportionate disruption to their lives in their most formative years during the pandemic [2].

According to some authors, the reduction in viral transmission is not a pre-eminent cause that eclipses all other potential harms, including children's physical, psychological and psychosocial well-being [3].

Among the many symptoms and physiological changes while wearing a face mask, an elevated blood carbon dioxide level is an important cornerstone of the so-called Mask-Induced Exhaustion Syndrome (MIES) [48]. There are several general short-term effects on human health due to low level CO<sub>2</sub>-inhalation: Physiological changes already occur at levels between 0.05% and 0.5% CO<sub>2</sub> showing increased heart rate, increased blood pressure and overall increased circulation with the symptoms of headache, fatigue, difficulty concentrating, dizziness, rhinitis, and dry cough [55]. While the effects of short-term exposure on cognitive performance begin at 0.1% CO<sub>2</sub> levels, with reduced cognitive performance, impaired decision-making and reduced speed of cognitive solutions, many other long-term effects are known at concentrations above 0.5% [55,56]. Exceeding the limit of 1% CO<sub>2</sub> the harmful effects include respiratory acidosis, metabolic stress, increased blood flow and decreased exercise tolerance [55]. Therefore, regarding low-level CO<sub>2</sub> exposition an EN149:2001+A1 (European Standard Norm) and a NIOSH (National Institute for Occupational Safety & Health) norm exist. A health-critical limit is set at 15 minutes for 3% for short periods, while the 8-hour limit is set at 0.5% CO<sub>2</sub> [57].

With female submarine crews entering the U.S. Army in November 2011, a reassessment of CO<sub>2</sub> limits was conducted back in 2012, focusing on potential reproductive and developmental effects. Inspired by this US Navy report on potentially harmful CO<sub>2</sub> values for female submarine crews based on animal studies [58] and the fact that increased CO<sub>2</sub> concentrations are inhaled while wearing face masks [48] the idea arose to conduct a scoping review. The aim of our review was to investigate the toxicological effects of face masks in terms of CO<sub>2</sub> rebreathing on developing life, specifically for pregnant women, children, and adolescents.



## 2. Methods

Our scoping review is based on a systematic literature search in MEDLINE, Cochrane Library and the World Health Organization COVID-19 Database up until 30<sup>th</sup> November 2021 on toxic effects of low-level carbon dioxide ( $\leq 3\%$ ) including mask effects on carbon dioxide breathing. Only English- and German-language peer reviewed records were considered that explicitly describe the toxicity of carbon dioxide at low concentrations as well as studies quantifying carbon dioxide when wearing masks under everyday conditions. Medical surgical masks on the one hand and N95 masks (FFP2 masks) on the other were of interest here. Search terms according to the criteria defined in the PICO scheme included [59]: “carbon dioxide”, “breathing” and “toxicity” as well as “carbon dioxide” and “mask”, including “surgical” and “N95”. We searched PubMed and Google Scholar for additional articles of interest. Two independent researchers identified and screened the eligible studies. The selected papers were checked by all authors for final eligibility. To expand the amount of published data further we reviewed citations from included articles to identify additional research.

Inclusion criteria were studies dealing with CO<sub>2</sub> breath concentrations below or equal to 3% and its effects. We based this threshold on the legal requirements for short-term exposure limits (15 min) [57]. Interventional studies were reviewed inspired by the Cochrane Collaboration's manual "Assessment of the risk of bias in clinical studies" (Cochrane RoB-2) [60]. Observational studies were reviewed inspired by the CASP (Critical Appraisal Skills Program) using standardised forms [61]. Work that did not relate to the research objective as described above or where there were no results relating to CO<sub>2</sub> was excluded. Animal and human experiments as well as modeling and test-suite measurements were included if the above criteria were met. Letters to the editor and case reports were not considered. Reviews found as part of the search strategy were used to objectify, verify, and classify the findings. Of the eligible papers, one with methodological weaknesses and one retracted paper were ultimately excluded.

The qualitative inclusion criteria for studies were: Valid reproducible presentation of the outcomes, comprehensible recruitment, confounders which were taken into account, credibility of the results, transferability to other populations, clear focus and comparability with existing evidence.

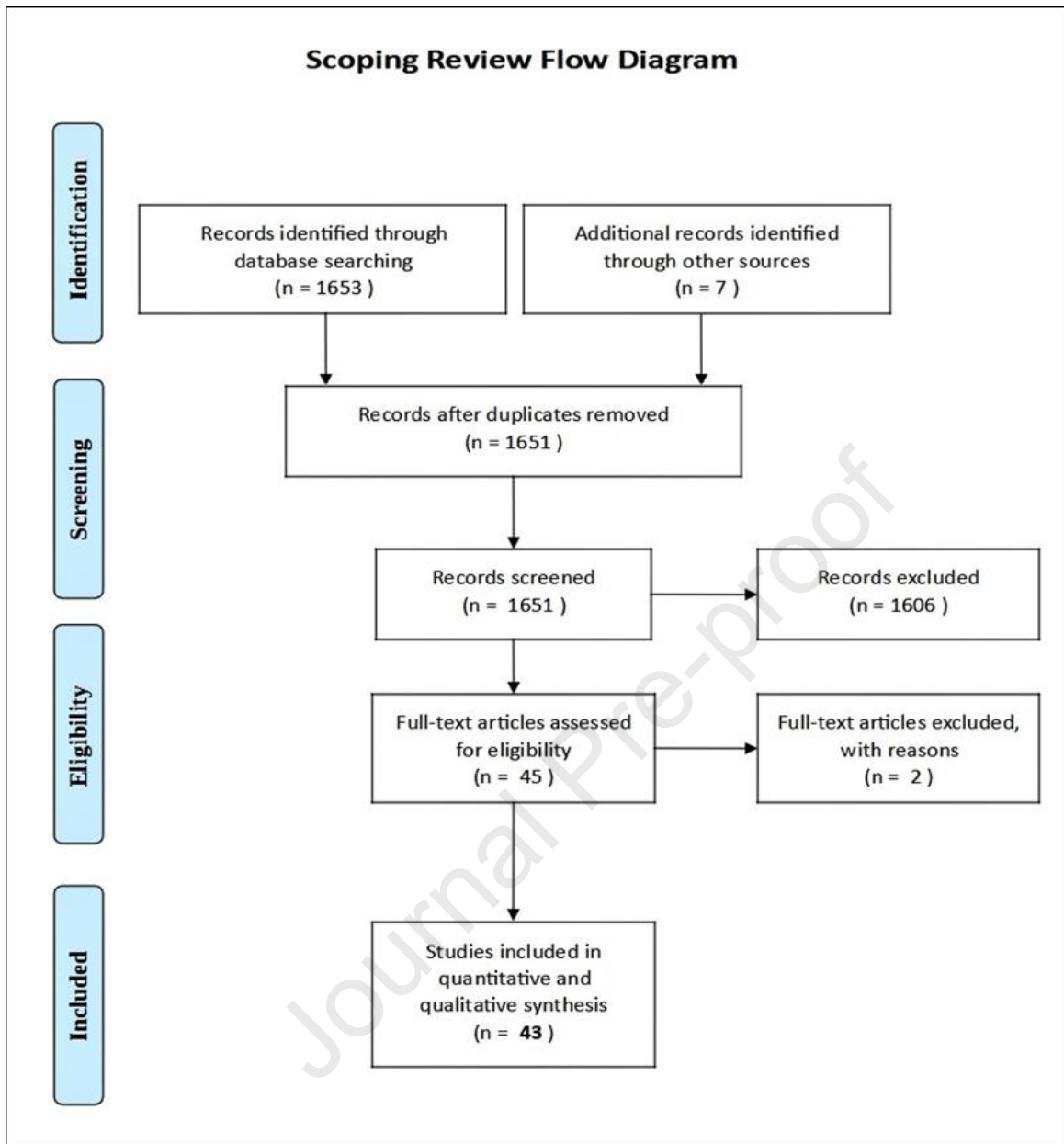
The quantitative inclusion criteria were: Appropriate methods, valid measurement of exposure, valid measurement of outcomes (continuous measurement of physiological parameters in all subjects of the study, including CO<sub>2</sub>), equality of groups, and sufficient size.

### 3. Results

The search yielded 1651 papers, of which 43 publications (2.6%) were finally considered for evaluation. This is not an unusually low rate in reviews. To name just a few examples with reviews cited by us: 1878 search results vs 6 selected (0.3%) [18], 2617 vs 31 (1.2%) [62], 1967 vs 17 (0.9%) [63]. Our selection of 2.6 % of the publications for the evaluation was strictly based on the inclusion and exclusion criteria and the quality assessment applied, which is described in detail in the methods section.

In addition to 25 mask experiments in humans, we found 2 modeling and 2 test suite measurements of CO<sub>2</sub> when using a mask. Four reviews describe the toxicity of inhaled low level CO<sub>2</sub>. From the referenced literature, two of the human and eight of the animal experiments examined the toxicity of carbon dioxide at low concentrations. The literature found demonstrates and quantifies in detail the effect of the face masks in terms of carbon dioxide rebreathing. It also describes in detail the effects of low concentration carbon dioxide toxicity. Figure 1 shows the flow chart of our scoping review.

**Figure 1.** Flow diagram according to the PRISMA scheme.



### 3.1. Effects of masks on carbon dioxide re-breathing

In the study of Ulrike Butz's dissertation [64] (an internally peer reviewed scientific publication) focusing on possible re-breathing of carbon dioxide in 15 healthy adult male volunteers, a carbon dioxide partial pressure of up to 21-24 mmHg was found under a surgical mask after 30 minutes [64]. This corresponds to about 2.8 - 3.2 % carbon dioxide of the inhaled air under the mask.

In Pifarrés mask-experiments of 8 adult females and males, a health-critical value of carbon dioxide concentration (CO<sub>2</sub> Vol%) was measured in the air under the masks after few minutes. The concentrations of 14162 ppm with a mask versus 464 ppm without a mask were statistically significant with  $p < 0.001$  increased by a high factor compared to the initial value (ambient air) and even more following exercise [65]. According to these experiments, masks can be responsible for a greatly increased CO<sub>2</sub> concentration of the inhaled air, which roughly corresponds to 1.41-1.7% carbon dioxide in inhaled air under the face mask ( $p < 0.001$ ) [65].

A project at the University of Delft used a validated method that clearly demonstrated that carbon dioxide re-breathing under standardised laboratory conditions (test suite) after 1 minute is at least 0.9% CO<sub>2</sub> for N95/ FFP2 masks [66]. Those elevated carbon dioxide levels of inhaled air, particularly under N95 masks, were also found in physiologically relevant short-time modeling studies. This confirms a constant increase leading to an averaged 1% inhaled CO<sub>2</sub> per breath during simulations of eight breathing cycles in 33.65 seconds [67] (see Figure 8 of mentioned publication with animation of CO<sub>2</sub> distribution with and without a respirator). Another modeling study shows that wearing N95 masks results in carbon dioxide accumulation, the volume fraction of CO<sub>2</sub> reaches 1.2% after 7 breathing cycles and is then maintained at 3.04% on average. The wearers re-inhale excessive CO<sub>2</sub> with every breath taken from the mask cavity [68].

In 2013 Sinkule already evaluated 30 different N95 respirators using the NIOSH Automated Breathing and Metabolic Simulator (ABMS) through 5 minute work rates and found elevated CO<sub>2</sub> levels in the inhaled air ranging between 1.28% and 3.52% [69]. These results are consistent with measurements of CO<sub>2</sub> in the dead space of the masks from experimental studies in humans with values of 2.8 [70] and 3.2 % [71].

In a self-experiment in 2020 Geiss measured the air under masks under laboratory conditions and only found an accumulation of carbon dioxide between 0.22 and 0.29% within 5 minutes mainly under surgical masks [72].

In a prospective observational study in 2021, Rhee examined the carbon dioxide concentration of 11 healthy volunteers during regular breathing and sitting at rest while they put on different types of masks for 15 minutes. Serial CO<sub>2</sub> measurements were performed with a nasal cannula at a frequency of 1 Hz [73]. The measured 2.4-2.6% CO<sub>2</sub> concentration translates into a highly significant increase in CO<sub>2</sub> with a KN95 respirator and a valved respirator at the nasolabial fold ( $p < 0.0001$ ), which is much greater than the NIOSH 8h threshold limit value [57]. The National Institute for Occupational Safety and Health (NIOSH) has an 8h threshold limit value – time-weighted average recommended exposure limit (TLV-REL) of 0.5% – and a 15 min threshold limit value – short-term exposure limit (TLV-STEL) of 3% for CO<sub>2</sub> – in workplace ambient air [57]. Rhee's quality study (serial CO<sub>2</sub> measurements with a high performance CO<sub>2</sub> sensor at a frequency of 1 Hz for 15 min) demonstrates a significant increase in end-tidal CO<sub>2</sub> concentrations among healthy volunteers while donning KN95 respirators. Consequently, the authors recommended further studies.

Table 1 summarizes the experimental findings concerning CO<sub>2</sub>-re-breathing under face masks.

**Table 1.** Experimentally measured CO<sub>2</sub> concentrations in the inhaled air under masks.

Experimental mask study	Analyzer type	Placement CO <sub>2</sub> sensor / sampling	Inhaled Vol% of CO <sub>2</sub> (mask wearing time)	Factor of increase*
<b>Blad 2020</b> [66] <i>FFP2/N95 and FFP3 masks</i>	GSS Sprint IR-WF-20	close to the breathing orifice	<b>0.42 - 0.94 %</b> <i>test suite</i> measurements (1 minute)	11 - 24
<b>Butz 2005</b> [64] <i>surgical masks</i>	RADIMETER TCC3	close to mouth on cheek	<b>2.8 - 3.2 %</b> measurements on <i>humans</i> (30 minutes)	70 - 80
<b>Geiss 2020</b> [72] <i>surgical masks</i>	TSI 7545 IAQ Meter	above nose tip, on nose bridge	<b>0.22 - 0.29 %</b> measurement on <i>human</i> (5 minutes)	6 - 7
<b>Laferty 2006</b> [70] <i>N95 masks</i>	Control Technologies GEM-500	inner side of face piece	<b>2.8 %</b> measurement on <i>humans</i> (7 minutes)	70
<b>Pifarré 2020</b> [65] <i>mask type not given</i>	Multi-Rae gas analyzer	not given	<b>1.41 - 1.7 %</b> measurements on <i>humans</i> (5 to 7 minutes)	35 - 43
<b>Rhee 2021</b> [73] <i>N95 masks</i>	GASLAB CM-0123 ExplorIR-W	at nasolabial fold	<b>2.4 - 2.6 %</b> measurements on <i>humans</i> (15 minutes)	60 - 65
<b>Roberge 2010</b> [71] <i>N95 masks</i>	p61-B, AEI	at nasolabial fold	<b>2.8 - 3.2 %</b> measurements on <i>humans</i> (60 minutes)	70 - 80
<b>Sinkule 2013</b> [69] <i>N95 masks</i>	NIOSH ABMS	close to the breathing orifice	<b>1.28 - 3.52 %</b> <i>test suite</i> measurements (5 minutes)	32 - 88

\*compared to normal air concentration with 0.04 Vol% CO<sub>2</sub>.

When masks are used elevated CO<sub>2</sub> concentrations are inhaled [64–73]. It also has the potential to exceed acute (3% CO<sub>2</sub> for 15 minutes) and chronic (0.5% CO<sub>2</sub> for 8 hours) NIOSH limits for CO<sub>2</sub> respiration (Table 1). Despite the compensatory mechanisms that occur (e.g. lowered blood pH, increased respiratory rate and ventilation) [74,75] an arterial PaCO<sub>2</sub> rise is inevitable in the long term [76]. For example, breathing air with an inspired CO<sub>2</sub> fraction of 1% ( $\approx$  8 mmHg) will increase arterial carbon dioxide by 1 mmHg, which increases ventilation at rest [74]. In a recent scoping review numerous important studies which provide statistically significant evidence for such CO<sub>2</sub> retention under the mouth-nose protection have been presented [48] and we have found additional studies that reveal scientific evidence of a carbon dioxide increase in the blood when masks are used.

In total, significant changes ( $p < 0.05$ ) could be found in most of the evaluated studies that measured body CO<sub>2</sub> content during mask use [64,76–91] (Table 2). Experiments with relatively short evaluation times [92] and pitfalls in their designs, e.g. taking of venous blood samples for measurement of blood gas parameters only if desired by the study participants, but not in all subjects [93] or using of a fan placed 30 cm before the mask and participants' face [94], showed no effects caused by masks. One of these studies was excluded due to shortcomings already mentioned in the methodological design related to CO<sub>2</sub> outcomes [93]. However, some studies with continuous measurement of physiological parameters including PtCO<sub>2</sub> in all subjects also found no statistical difference between mask and no mask use, though measured CO<sub>2</sub> levels were continuously higher in mask wearers [71,95]. Some of these studies were conducted under extreme conditions (1 hour of treadmill exercise at ambient conditions of 35°C and relative humidity 50%) and within selected user groups (e.g. young healthy, nonsmoking men) [96]. Overall, the most prominent rise in CO<sub>2</sub> was observed while wearing N95 masks. In the literature found, this phenomenon is attributed to the fact that the dead space volume is almost doubled and the breathing resistance is more than doubled, which leads to a significant re-breathing of CO<sub>2</sub> with every breathing cycle [48,67,68]. Due to compensatory mechanisms, carbon dioxide partial pressure (PaCO<sub>2</sub>) in the blood is at a sub-threshold generally in healthier people [74,76], but in sick people a partially pathological increase is detected [81]. However, all mask types like community masks, surgical mask, as well as N95 respirators can be responsible for a significant and comparable rise in the blood content of CO<sub>2</sub> [79].

In summary, the build-up of CO<sub>2</sub> behind the masks is predominantly within the short-term exposure limits of NIOSH and EN149 [57,65,66,70,73]. However, wearing face masks has the potential to exceed chronic (0.5% CO<sub>2</sub> for 8 hours) [64–66,69–71,73] and even acute (3% CO<sub>2</sub> for 15 minutes) [64,69,71] NIOSH limits for carbon dioxide respiration (Table 1).

Table 2 shows studies revealing evidence of carbon dioxide retention when masks are used.

**Table 2.** Significant increase in CO<sub>2</sub> levels in mask wearers under various conditions in scientific intervention studies.

Experimental mask study Author & Year	Parameter	CO <sub>2</sub> outcome in mmHg* No vs Mask	Rise mmHg	P -value
<b>Bharatendu 2020</b> [77]	PETCO <sub>2</sub>	N95 masks: 37.3 vs <b>40.4</b>	<b>+3.1</b>	<0.001
<b>Butz 2005</b> [64]	PtCO <sub>2</sub>	surgical masks: 40 vs <b>45.6</b>	<b>+ 5.6</b>	<0.05
	PCO <sub>2</sub>	under surgical mask: 0.31 vs <b>22.49</b>	<b>+22.18</b>	<0.05
<b>Dirol 2021</b> [89]	PETCO <sub>2</sub>	surgical masks: 37.2 vs <b>38.7</b>	<b>+1.5</b>	<0.001
<b>Epstein 2020</b> [78]	PETCO <sub>2</sub>	surgical masks: 35 vs <b>40</b>	<b>+5</b>	<0.03
	PETCO <sub>2</sub>	N95 masks: 35 vs <b>43</b>	<b>+8</b>	<0.001
<b>Georgi 2020</b> [79]	PtCO <sub>2</sub>	community masks: 38.4 vs <b>39.1</b>	<b>+0.7</b>	<0.001
	PtCO <sub>2</sub>	surgical masks: 38.4 vs <b>39.9</b>	<b>+1.5</b>	<0.001
	PtCO <sub>2</sub>	N95 masks: 38.4 vs <b>40.5</b>	<b>+2.1</b>	<0.001
<b>Kim 2013</b> [90]	PtCO <sub>2</sub>	N95 masks: 39.7 vs <b>42.7</b>	<b>+3</b>	<0.01
<b>Kyung 2020</b> [80]	PETCO <sub>2</sub>	N95 masks: 24.8 vs <b>25.7</b>	<b>+0.9</b>	<0.001
		34.0 vs <b>35.5</b>	<b>+1.5</b>	<0.001
<b>Lubrano 2021</b> [86]	PETCO <sub>2</sub>	N95 masks: 32 vs <b>39</b>	<b>+7</b>	<0.005
<b>Mapelli 2021</b> [88]	PETCO <sub>2</sub>	surgical masks: 33 vs <b>35.1</b>	<b>+2.1</b>	<0.05
		N95 masks: 33 vs <b>36.3</b>	<b>+3.3</b>	<0.05
<b>Mo 2020</b> [81]	PaCO <sub>2</sub>	surgical masks: 40.77 vs <b>49.75</b>	<b>+8.98</b>	<0.005
<b>Pifarré 2020</b> [65]	PCO <sub>2</sub>	under masks: 0.35 vs <b>10.76</b>	<b>+10.41</b>	<0.001
	PCO <sub>2</sub>	under masks: 0.35 vs <b>12.92</b>	<b>+12.57</b>	<0.001
<b>Rebmann 2013</b> [82]	PtCO <sub>2</sub>	N95 masks: 32.4 vs <b>41.0</b>	<b>+8.6</b>	<0.01
<b>Roberge 2012</b> [83]	PtCO <sub>2</sub>	surgical masks: 39.31 vs <b>41.48</b>	<b>+2.17</b>	<0.001
<b>Roberge 2014</b> [84]	PtCO <sub>2</sub>	N95 masks: 31.3 vs <b>33.3</b>	<b>+2</b>	<0.05
<b>Tong 2015</b> [85]	FeCO <sub>2</sub>	N95 masks: 25.84 vs <b>28.12</b>	<b>+2.28</b>	<0.001
<b>Zhang 2021</b> [87]	PETCO <sub>2</sub>	surgical masks: 38.8 vs <b>41.6</b>	<b>+2.8</b>	<0.001

PaCO<sub>2</sub>=Arterial partial pressure of CO<sub>2</sub>, PCO<sub>2</sub>=Partial pressure of CO<sub>2</sub>, PETCO<sub>2</sub>=End-expiratory partial pressure of carbon dioxide, PtCO<sub>2</sub>=Percutaneous CO<sub>2</sub>, FeCO<sub>2</sub>=Exhaled CO<sub>2</sub>. \*If necessary, values have been standardised for comparability, assuming normal values of CO<sub>2</sub> content of room air (409 ppm) and normal air pressure (760 mmHg) according to the formula:

Vapor Pressure (mmHg) =  $\frac{\text{Atmospheric Pressure (mmHg)}}{10^6} * \text{ppm}$ . Please Note: Breathing air with inspired CO<sub>2</sub> fraction of 1% ( $\approx 8$  mmHg) will increase arterial carbon dioxide (PaCO<sub>2</sub>) by 1 mmHg, [28]. PETCO<sub>2</sub> and PtCO<sub>2</sub> measurements provide an estimation of PaCO<sub>2</sub> [97–99].



### 3.2. General effects of CO<sub>2</sub> breathing in low concentrations ( $\leq 3\%$ )

From a toxicological point of view, carbon dioxide is absorbed passively through the lungs from the breathed-in air. Human metabolism also produces carbon dioxide, which naturally requires elimination. Carbon dioxide is largely carried in the blood as bicarbonate, which is catalysed by the enzyme carbonic anhydrase. The excretion is accomplished mainly via the lungs although the kidneys also excrete small amounts. In expert literature, concentrations of  $>2\%$  carbon dioxide in inhaled air are expected to cause adverse health effects [100]. Often after a short exposure of CO<sub>2</sub> levels above 1% an increase in cardiac output is seen. Inhalation of between 2.5–3.5% carbon dioxide for up to 10 minutes may increase the cerebral blood flow up to 100% and the dilatation of cerebral blood vessels may be responsible for the severe headache produced [77,100]. Exposure to increased carbon dioxide concentrations causes hyperventilation. Interestingly, due to compensatory mechanisms such as lowered blood pH, increased respiratory rate and ventilation, acclimatisation occurs with chronic low concentrations of carbon dioxide [74,75,100]. Acute symptoms usually resolve despite continuing exposure of carbon dioxide at concentrations of up to 3%. However, in healthy adults metabolic changes are responsible for slight long-term damages (changing cellular pH, disturbing normal homeostasis of the cells leading to an acidosis and N-carboxy derivatives of peptides, proteins, and amino acids) at concentrations of  $<5\%$  [100].

Some mechanisms of human adaptation to low-level exposure of CO<sub>2</sub> had been evaluated experimentally including levels of 1-2% [74,75]. Regarding the referenced mask literature those carbon dioxide values of 1-2% can be assumed for masks [64,65,67–71,73]. In the human experiments with low level 1-2% CO<sub>2</sub> exposure an increased respiratory minute volume of more than 34% was detected [75]. Moreover, higher arterial PaCO<sub>2</sub> and bicarbonate levels produced an effective buffering of inhaled CO<sub>2</sub>. A correlation could be shown between changes in plasma calcium level, pH, and CO<sub>2</sub>, indicating that the bone CO<sub>2</sub> store is a determining factor in the extended time periods

of CO<sub>2</sub> retention and elimination. Kidney and organ calcification was frequently seen in animal studies, emphasising the involvement of calcium metabolism in adaptation to elevated levels of carbon dioxide [56,75,101–104]. A comprehensive review reported carbon dioxide in relationship with chronic and/or intermittent long-term exposure conditions that might induce pathological states, in particular favouring DNA alterations, nasal inflammation, and pulmonary inflammation [56].

### **3.3. Circumstantial evidence for specific mask effects: Low-level inhaled CO<sub>2</sub> toxicity in animal studies**

One principle of toxicological consideration of the risk of exposure to noxious agents to humans is the use of evidence from animal studies. Therefore, the most important animal studies on carbon dioxide respiration at low concentrations ( $\leq 3\%$ ) are presented. They provide information on possible mask effects. It should be mentioned that in a great work of toxicology [105] the following statement on page 156 can be found: "Small laboratory animals (mice) cannot serve well as indicators for carbon dioxide as they do for carbon monoxide, since they are much less sensitive to it than humans". Therefore, in an appropriate risk assessment it is necessary to apply an inter-species uncertainty factor.

#### **3.3.1. Low level CO<sub>2</sub> inhalation: Teratogenicity and stillbirth**

From decades of studies on the toxicity of carbon dioxide it is known that just 0.5% carbon dioxide for a few minutes to an hour per day is capable of inducing stillbirth and teratogenic birth defects in guinea pigs [106] (Page 14 of the referred FDA document). People in positions of responsibility in the US Navy have been aware that this level of 0.5% carbon dioxide in submarines is often exceeded. They therefore set up a study in pregnant rats, the details of which have been published [58,107]. In rats the first signs of toxicity to pups were observed at a level of 3% carbon dioxide exposure for the pregnant dam with no signs of toxicity at 2.5% exposure. In the 3% CO<sub>2</sub> exposure group the findings

were a statistically significant mean litter proportion of post-implantation loss (resorptions occurring in the early phase of pregnancy) and a corresponding statistically significant lower mean litter proportion of viable foetuses. Moreover, they found one foetus had gastroschisis (stomach, several loops of the intestine and liver protruding through an opening in the ventral midline) and localised foetal oedema was noted in 2 other foetuses: one of the hind limbs and the other of the neck and thorax. With a safety factor between animals and humans of about three, the US Navy toxicity experts then set the exposure limits for submarines carrying a female crew to 0.8% carbon dioxide as well as emergency exposure with a limit of 24 hours [58,107].

### **3.3.2. Low level CO<sub>2</sub> inhalation: Neurotoxicity**

To figure out the negative impact of poor indoor air quality on early brain development a research study exposed pregnant rats [108] to carbon dioxide levels of 0.1 to 0.3 %, which is unfortunately commonplace in poorly ventilated closed buildings [55]. At an exposure of 0.3% carbon dioxide for the pregnant rats the pups demonstrated reduced spatial learning and memory at the age of approx. 6 weeks [108]. This reduced spatial learning and memory was attributed to histologically proven damaged neurons in a part of the brain called the hippocampus [108]. This damage is irreversible and it affects mental health in the long term. When the pregnant rats were exposed to just 0.1% CO<sub>2</sub> the pups demonstrated increased anxiety [108], which is even more pronounced when the pregnant mother animals were exposed to 0.3% CO<sub>2</sub>.

Carbon dioxide exposure, depending on its duration and intensity can cause oxidative stress [109]. Oxidative stress mediates apoptosis by forming lipid hydroperoxides that are highly toxic and cause DNA fragmentation [110]. This condition causes mitochondrial damage, which can lead to a release of Cytochrome C, Caspase activation and finally cell death [111].

Low indoor air quality in classrooms is well known to be associated with a negative impact on the learning capacity of school children [55,56,112]. To establish whether this only indicates a short-term effect or possible substantial damage to brain function, a study in mice was performed and published [113]. Adolescent mice were exposed 24 hours a day for 7 weeks to a level of 0.3% carbon dioxide, but with normal atmospheric levels of oxygen [113]. At the end of the study a so-called water maze exercise was performed. Here the mice have to find a life-saving platform in a water basin. This test distinguishes between impact on physical function and on mental function. Mice were tested on four consecutive days. On the first test day mice in all groups (carbon dioxide exposed and normal air exposed) typically needed around 40 seconds to find the platform. Healthy mice exposed to normal air learned to find the platform more quickly and after four days the healthy mice finally only needed 20 seconds to find the platform, whereas the carbon dioxide exposed mice were unable to learn the shortest way to the platform. Although the carbon dioxide exposed mice were able to swim as quickly as their healthy controls, they were not able to learn the shortest route. They swam around in a very disoriented manner day after day of the four test days. Histology tests demonstrated apoptosis of brainstem neurons in those 0.3% carbon dioxide exposed mice [113]. This is a very disturbing finding because this CO<sub>2</sub>-induced loss of neurons is irreversible.

### **3.3.3. Low level CO<sub>2</sub> inhalation: Male reproductive toxicity**

As a rise in carbon dioxide when wearing a mask is scientifically proven (Tables 1 and 2) [64–73,76–91], further information about the phenomenon of the toxicological influence of elevated carbon dioxide of inhaled air on male fertility needs to be given. The toxic effects of low-level carbon dioxide exposure on male fertility have been studied extensively in animal experiments. The exposure of adolescent rats to a carbon dioxide level of 2.5% once for four hours induced pathological signs of diminished fertility in rat testes [114]. A correct estimation of an exposure limit from animal toxicity studies to humans requires implementation of a safety factor [58,107,115]. One

has to consider that small laboratory animals, evolutionarily adapted to living in burrows and caves, are limited as indicators for carbon dioxide, since they are much less sensitive to it than humans [105]. As aforementioned, the US Navy was using a safety factor of 3 from a level with no adverse effects on rat pregnancies [58,107]. In the study referred to on rat testicular function of carbon dioxide no so-called NOAEL (No-Observed-Adverse-Effect-Level) was observed [114]. Using the 2.5% level with marked damage to testes function and a minimum safety factor of 5, an exposure limit for adolescent males needs to be set at 0.5% for a maximum of 4 hours a day [58,107,114,115].

Table 3 sums up the significant toxicity of inhaled carbon dioxide at low levels in animal studies.

**Table 3.** Significant toxicity of inhaled carbon dioxide at low levels in animal studies.

<b>Experimental study, <i>species</i></b>	<b>Toxic CO<sub>2</sub>-level (Vol%) [exposure duration]</b>	<b>Significant Outcome</b>
<b>FDA Technical Reports 1979</b> [106] <i>guinea pigs</i>	<b>0.48 %</b> Exposure to pregnant [10 min over 20 days each]	Stillbirth and birth defects (67.5%)
<b>Howard 2012</b> [58] <i>rats</i>	3% resp. <b>0.8 %*</b> Exposure to pregnant [chronically]	Stillbirth and birth defects (p<0.01)
<b>Kiray 2014</b> [108] <i>rats</i>	<b>0.3 %</b> Exposure to unborn (pregnant) [chronically]	Neuron destruction in prefrontal cortex and hippocampus, decreased IGF-1 levels, increased anxiety after birth, impaired memory and learning (p<0.05)
<b>Uysal 2014</b> [113] <i>mice</i>	<b>0.3 %</b> Exposure to adolescent [chronically]	Neuron destruction in gyrus dentatus and the prefrontal cortex, decreased IGF-1 levels, less activity, increased anxiety, impaired learning and memory (p<0.05)
<b>Vandemark 1972</b> [114] <i>rats</i>	2.5 % resp. <b>0.5 %*</b> Exposure to male [4 hours]	Destruction of spermatid and Sertoli cells in testes, streaking & vacuolization of the tubular components, no maturation of spermatids (histopathological proof)

\*calculated for humans with an interspecies safety factor, for further details see Howard et al [58,107,115].

## 4. Discussion

The above data including Table 1, Table 2 and Table 3 indicate that mandatory daily long-term use of masks (surgical, N95), especially for children, adolescents, younger people and pregnant women can lead to negative effects. With reliable measurements the experimentally determined CO<sub>2</sub> concentrations in the inhaled air under masks can reach – depending on exposure time – values of 0.42 up to 3.52 Vol% (Table 1) [64–66,69–71,73]. One has to remember, that in those experiments the time measured wearing a mask ranged from 1 minute to several minutes with a maximum of 60 minutes in a few studies, which is not always representative for real-world settings. Nevertheless, the results of our review show that mask use can lead to levels exceeding the NIOSH and EU Indicative Exposure Limit Values in Directives, both acutely and chronically [57,116].

### 4.1. Consequences for pregnant women and early life (unborn)

For pregnant women there is a metabolic need for a foetal-maternal CO<sub>2</sub> gradient. The mother's blood carbon dioxide level should always be lower than that of the unborn child. This is necessary to ensure the diffusion of CO<sub>2</sub> from the foetal blood into the maternal circulation via the placenta. Therefore, the hypercapnic gas shifts promoted by masks could, even with subliminal carbon dioxide increases, act as an interference variable of the foetal-maternal CO<sub>2</sub> gradient and increase over time of exposure [48]. Thus, even if compensatory mechanisms are active [74,75], an additional risk for pregnant women and their unborn children must be considered. Comparative studies show significantly higher CO<sub>2</sub> levels in pregnant women wearing N95 masks [84,85]. It is well-known from many disciplines that the toxicity of a pollutant depends on the one hand on the concentration and on the other on the duration of exposure. The frequency of exposure and time are of toxicological importance and there is the notion, that time is a variable equivalent to dose in toxicology [117,118]. According to Rozman, risk projecting should include time as a variable (including toxicokinetic, toxicodynamic,

exposure frequency/duration). Adding time to dose as an independent variable in toxicology allows a risk assessment in which a single acute dose would represent the liminal case when the dose rate equals the dose. Consequently, the effects of a single high dose exposure will not differ from exposure to proportionally smaller but chronic doses, e.g. daily dose rates [117,118]. This goes hand in hand with Haber's rule of inhalation toxicology [117], simply known as  $c \times t = K$ , where  $c$  is the concentration of the gas,  $t$  the amount of time necessary to breathe the gas and  $K$  is the constant depending on the gas and the effect. Exceptions are accounted for the experimental protocol by specifically invoking kinetics (rate of depuration of the active toxicant via metabolism and elimination) vs dynamics (time to recovery from the effects of the toxicant) where the mathematical relationship can also be described as:  $c^n \times t^m = K$ , with  $n$  and  $m$  being toxicant-specific exponents [119]. This rule states that time and not only concentration (dose) is an important factor in toxicological considerations (going beyond Paracelsus, who only considers the dose). In other words, even low but chronic or intermittent exposure to toxins (without sufficient time for compensation) can show cumulative adverse effects and thus toxicologically relevant changes similar to those in shorter but higher doses [117]. For example, it is known from human experiments, that, intermittent exposure to CO<sub>2</sub> does not allow the compensation mechanisms to be active [56]. For the same carbon dioxide concentration (dose), acute exposure is less problematic than chronic or intermittent exposure. According to Haber's rule, however, a chronic, lower dose can also correspond to the effect of an acute but higher (threshold) dose. This approximate relationship also results, for example, in the different NIOSH limits for 8 h (0.5% CO<sub>2</sub>) and 15 min (3% CO<sub>2</sub>) exposure times [57].

Additionally, one has to consider the special susceptibility of early life conceptual tissues with less well-developed protective/conjugative pathways [53].

However, taking into account the above facts of increased carbon dioxide rebreathing under masks with values ranging from 0.22 to 3.52 vol% CO<sub>2</sub> in the majority of studies with values above 1%



[64,65,67–71,73] including Table 1, it is clear that carbon dioxide rebreathing, especially when using N95 masks, is above the 0.8% CO<sub>2</sub> limit set by the US Navy to reduce the risk of stillbirths and birth defects on submarines with female personnel who may be pregnant [58,106,107] (Table 3). One has to keep in mind that US Navy female submarine officers are of very high mental and physical fitness [120,121], different to the level of physical health of pregnant women in the broad population. Nowadays all over the world masked pregnant women (especially those using N95 masks) are potentially exposed to carbon dioxide re-breathing levels that are prohibited by US Navy for female submarine officers because of the risk of stillbirth and birth defects. Analysis of online available data on mask mandates [1] show, according to our calculations, that most countries (150 out of 194) worldwide had a masking requirement (77.3%) roughly corresponding to 4 496 149 755 people worldwide accounting for 58% of the world population.

So one has to ask: May there be a link between an increased mask-related (pandemic) global carbon dioxide re-breathing since 2020 and the current reported disturbing 28% rise in stillbirths worldwide [62]? In a prospective registry of 263 infants of 179 infected mothers the authors found no evidence that a SARS-CoV-2 infection is associated with significant higher risk of damage to unborn life [122]. However, current data on the new Delta variant, imply a possible slightly higher risk of stillbirths (prepandemic stillbirth rate of 0.59% versus 0.98% in COVID-19-affected deliveries and 2.70% during the Delta period), but the evaluation was not able to separate SARS-CoV2 exposure from higher mask exposure in those women [123]. Interestingly, recent data from Australia shows that lockdown restrictions and other measures (including masks that have been mandatory in Australia), in the absence of high rates of COVID-19 disease, were associated with a significant increase in preterm stillbirths [124]. May there be also a link between the pandemic driven excessive mask-use and the fact that 42% of female USA surgeons surveyed between November 2020 and February 2021 [125] lost a pregnancy according to a recent study? During a pandemic, surgeons are

likely to have the heaviest mask exposure compared to the general population. Data from Italy show a three-fold increase with statistical significance in stillbirths in the general population during lockdown period (March-April-May) 2020 compared to the same period in 2019 [126]. A recent rapid review and meta-analysis gives clues about the severity of the indirect influence of COVID-19 lockdown implementations [63]. The authors found that lockdown measures were associated with a significant risk of stillbirth with RR=1.33 (95% CI 1.04, 1.69) when compared to before lockdown period [63]. It is well known that lockdown measures include mask mandates as well [19].

Among the few countries that do not require the wearing of masks in public is Sweden. Interestingly, despite similar pandemic measures and SARS-CoV-2 presence in the media and in the real world, no increased risk of stillbirths was observed in Sweden. A Swedish nationwide study “did not find any associations between being born during a period when many public health interventions aimed at mitigating the spread of COVID-19 were enforced and the risk for any of the preterm birth categories or stillbirth (adjusted OR 0.78, CI 0.57 to 1.06)” [127]. Although society was not completely closed, Swedish authorities enforced many policies to mitigate the spread of COVID-19, such as promotion of general hygiene measures and social distancing (including remote working), ban of non-essential travel, prohibition of gatherings of more than 50 people and the closure of upper secondary schools and universities [127].

A look at Table 3 shows that the results of the FDA (1979) [106] and Howard experiments (2012) [58,107] on toxic CO<sub>2</sub> levels may explain the increase in the incidence of stillbirths found in the above studies. Moreover, wearing N95 masks that are linked to a higher carbon dioxide re-breathing (Table 2) [78,79,88] is significantly more associated with higher gestational age than surgical masks (stronger N95 use than surgical mask) [128].

The exact mechanism of low-level CO<sub>2</sub> toxicity for unborn life is not known in detail. Maternal and foetal mechanisms have to be taken into account. With regard to the adverse maternal changes an increased CO<sub>2</sub> and acidity in the blood (pH changes) trigger various compensatory mechanisms. These include pH buffering systems in the blood, increased breathing to reduce excess CO<sub>2</sub> in the bloodstream, increased excretion of acid by the kidneys to restore pH balance and nervous system stimulation due to changes of heart contractibility and vasodilation [129,130]. During respiratory acidosis the kidneys retain bicarbonate helping to normalize the pH of the blood. With prolonged CO<sub>2</sub> stress a metabolic acidosis occurs and the kidneys no longer respond in producing bicarbonate [101]. Thereafter –with a further prolonged CO<sub>2</sub> burden – the body uses the bones to regulate the acid levels in the blood: Bicarbonate and a positive ion (Ca<sup>2+</sup>, K<sup>+</sup>, Na<sup>+</sup>) are exchanged for H<sup>+</sup>. The kidney tubule recovers filtered bicarbonate or secretes bicarbonate into the urine to help maintain the pH balance in the blood, which involves the Carbonic Anhydrase (CA) enzyme [131]. CA enzymes participate in metabolic reactions that convert CO<sub>2</sub> and result in the precipitation of calcium carbonate [102,103,132]. CA is involved in the calcification of human tissues including bone and soft-tissue calcification [102]. Carbon dioxide conversion by the CA enzyme provides bicarbonate and hydrogen ions that fuel the uptake of ionised calcium, which is then deposited in the body tissues as calcium carbonate. Increased CO<sub>2</sub> in the blood caused by breathing elevated levels of the gas could lower the pH enough to increase the activity of CA thereby potentially increasing calcium carbonate deposits [103]. Significant tissue calcification has been observed in animals after a 2-week exposure to 1% CO<sub>2</sub> or an 8-week exposure to 0.5% CO<sub>2</sub> with only slight reductions in pH [104]. This would occur by CA activity where tissues connect with plasma, e.g. arteries, kidneys or even the placenta. A placenta calcification is associated with a higher risk of adverse pregnancy outcomes [133–135]. This mechanism appears plausible as the final damaging step in the maternal body.

In addition, carbon dioxide is also known to play a role in oxidative stress caused by reactive oxygen species (ROS) [136]. This would impede foetal body development. In particular, oxidative damage to cellular DNA can lead to mutations [56,136].

Moreover, inflammation which can lead to serious illness that is known to be caused by low-level CO<sub>2</sub> exposure in humans and animals [56,112,137–139]. CO<sub>2</sub> increases the result in higher levels of pro-inflammatory Interleukin-1 $\beta$ , a protein involved in regulating immune responses, which causes inflammation and vascular damage [137]. Significant upregulation of IL-1 $\beta$  may be associated with an imbalanced immune system and a procoagulant state that could be responsible for early pregnancy loss [140]. The complex interplay of IL-1 $\beta$  at the fetomaternal interface and its crucial role in miscarriage processes has been studied including such elevated protein expression of IL-1 $\beta$  in the decidua using double-immunofluorescence [140]. In this case, both foetal as well as maternal vascular damages are to be expected.

Interestingly, a recent publication summarised a large on-going longitudinal study of child neurodevelopment in Rhode Island, an USA state with mask mandates, examining general childhood cognitive scores in 2020 and 2021 vs. the preceding decade, 2011-2019 [141]. The scientists found that children born during the pandemic have significantly reduced verbal, motor, and overall cognitive performance compared to children born pre-pandemic with consistent and significant reductions ( $p < 0.001$ ) showing lower cognitive skills [141]. Could there be a connection between the increased use of N95 masks by pregnant women [128], higher carbon dioxide re-breathing levels (Tables 1&2) [64–71,73,78,79,88] and the results [141] of this recent study? Fresh outdoor air has around 0.04% carbon dioxide [55,56] and the level of re-breathed CO<sub>2</sub> under masks can rise to levels far higher than 1% as mentioned above [64,65,67–71,73], especially when masks are worn in closed buildings additionally worsening the sick building syndrome [55,56]. A look at Tables 1 and 3 shows that the results of the Kiray 2014 [108] experiments could be an explanation of these findings due to

the fact that most human studies prove CO<sub>2</sub> exposition of higher than 0.3% while using a face mask. After low-level exposure of 0.3% CO<sub>2</sub> to the pregnant dams, Kiray was able to detect neuron destruction in prefrontal cortex and hippocampus, decreased IGF-1 levels, increased anxiety and impaired memory and learning of the offspring after birth [108].

#### **4.2. Consequences for children and adolescents**

The problem of prolonged mask use in children and in schools needs to be discussed as well. One has to consider that children are not just small adults. This means that exposure criteria should be based on information relevant to predicting risks to children and should account for such toxicokinetic differences occurring with development [53].

In this context, it is crucial to discuss the toxicological impact of prolonged mask wearing and the concomitant elevation in re-breathed carbon dioxide (Tables 1, 2 and 3). Regarding the experimentally measured CO<sub>2</sub> concentrations in the inhaled air under masks from Table 1 with values ranging from 0.22% to 3.52% being mostly above 0.3% [64–73], the results from Table 3 [113,114] are remarkable. In 2014 Uysal could demonstrate with his experiments that a mere 0.3 % CO<sub>2</sub> exposure to adolescent brain neurons can cause destruction in the gyrus dentatus and the prefrontal cortex with decreased IGF-1 levels resulting in less activity, increased anxiety and impaired learning and memory [113]. When exposure to low level CO<sub>2</sub> is prolonged (several hours to one week) the organism depletes its buffer systems [113,142–144]. The number of cells in the brain of adolescents is a result of the equilibrium of cell proliferation and apoptosis. External factors can affect both cell proliferation and death. In the case of prolonged low-level CO<sub>2</sub>-exposure the latter occurs, especially under exercise or stress [145–148]. Blood carbon dioxide concentration exerts an important influence on intra- and extracellular pH, CO<sub>2</sub> passes quickly through the cell membranes to form carbonic acid with H<sub>2</sub>O, which releases H<sup>+</sup> ions and, in excess, causes acidosis [149–151]. Acidosis decreases

transmembrane Ca<sup>2+</sup> conductivity and decreases the excitability of neurons [152,153]. Calcium overload causes excitotoxicity and apoptosis during hypoxia [154].

Already in 1972 Vandemark revealed – only after a 4-hour low level CO<sub>2</sub> exposure – a carbon dioxide dependent destruction of spermatid and Sertoli cells in testes, streaking & vacuolization of the tubular components with no maturation of spermatids [114]. Calculated with a human safety factor [58,107,115], the carbon dioxide content of the inhaled air should be at least below 0.5% CO<sub>2</sub> for a 4-h exposure to avoid these adverse effects on testicular tissue. According to data from Table 1, when wearing masks – for example in schools– this seems difficult to achieve in many cases [64–71,73] especially when room air (in crowded classrooms) already has an increased CO<sub>2</sub> content [55,56,112]. The damaging mechanism of CO<sub>2</sub> affecting testicular tissues is based on the conditions of oxidative stress and acidosis with increased inflammation and apoptosis as described above [109,110,112,136–139]. Testes metabolism and cell respiration have been shown to be inhibited increasingly by rising levels of CO<sub>2</sub> [114]. It has to be pointed out that this data on the toxicity of carbon dioxide on reproduction has been known for 60 years. Exposure limits have therefore typically been set at 0.5% CO<sub>2</sub> in working environments, e.g. according to a Safety Data Sheet by the Linde Company on Exposure Limits [116]. These limits are based on EU Indicative Exposure Limit Values in Directives 91/322/EEC, 2000/39/EC, 2006/15/EC, 2009/161/EU, 2017/164/EU. An 8-hour exposure limit of 0.5% CO<sub>2</sub> has been defined in the NIOSH regulations [57]. Looking at the potential damage to the reproduction function by subacute or chronic carbon dioxide exposure proven in animal experiments makes it very clear why these limits exist.

### **4.3. Consequences for science and supervisory authorities**

Altogether, there is disturbing experimental evidence for a possible negative impact risk on the mental and reproductive health of children, adolescents and early life (unborn) due to chronic carbon

dioxide re-breathing since the introduction of mask mandates (Table 1 and Table 3). Indeed, masks (being a medical device) for general and long-term use in the populace should be evaluated more thoroughly according to the German Medical Devices Act (Medizin-Produkte-Gesetz), the European MDR (Medical Device Regulation) and the FDA [57,155,156]. Other cultures have been wearing face masks long before COVID [157]. The prepandemic face mask wearing habits of such countries are not comparable to the pandemic face mask wearing requirements, but scientific data supports our hypotheses from sections 4.1. and 4.2. Even before the pandemic, in Asia the stillbirth rates have been significantly higher compared to e.g. Eurasia, Oceania or North Africa [158]. Additionally, in East Asia there is scientific evidence of fertility decline for decades [159] and an ultra-low fertility is also described [160].

In summary, benefits and risks of masks have to be assessed according to the WHO especially for children, pregnant women, the elderly and the ill [48,161].

The average lethality risk for children and young women of childbearing age for SARS-CoV2 is far lower than the average lethality risk for SARS-CoV2 [162]. In a recent study, no healthy children between 5 and 18 years of age were found to have died from COVID [163]. However, according to the data we found, there could be a developmental risk to healthy children and early life from prolonged mask wearing.

Indeed, if the potential adverse effects and possible long-term consequences of masks [48] are taken into account (Table 3) doubts arise regarding masks as a harmless means of combating SARS-CoV2 in widespread use, especially regarding our referenced data with possible deleterious effects for children, adolescents and pregnant women [58,64–71,73,106–108,113,114]. The background of the decisions on far-reaching mandatory mask use is difficult to understand scientifically [162].

According to the medical principle of "primum nihil nocere" (at first do not harm) and in view of the

presented findings, the mask would have to be scientifically re-evaluated as a SARS-CoV2 pandemic control. The credo of all those involved in the containment of the crisis should be to prevent the damage caused by precautionary or therapeutic measures at all costs so as not to exceed the damage caused by the disease. When it comes to medical decision-making in a sick person, the assessment of therapeutic measures for the benefit of the patient against the side effects of the therapy is to be evaluated differently than a prophylactic procedure in healthy people. If wrong decisions are made in the selection of preventive measures in healthy people or if they are improperly applied, the consequences are usually much more severe and liability claims are often unavoidable. In view of the possible toxicological mask effects of re-breathed carbon dioxide in pregnant women, children and adolescents, and in view of the limited scientific evidence for masks as an effective pandemic measure, there is need to re-evaluate and reconsider mask mandates especially for these vulnerable subgroups.

Further reliable studies on possible carbon dioxide re-breathing while wearing a mask in real-world scenarios are necessary to exclude possible damaging effects [62,63,124–126,141]. Therefore, health authorities should plan and perform further toxicological studies focusing on masks in specific user groups according to Good-Clinical-Practice and Good-Laboratory-Practice.

So far such mandatory activities by governments and health authorities have not been visible globally. Regarding the referenced literature, low level CO<sub>2</sub> exposure can be related to mask use. Keeping in mind the weak antiviral mask efficacy, the general trend of forcing mask mandates even for the vulnerable subgroups is not based on sound scientific evidence and not in line with the obligation in particular to protect born or unborn children from potential harmful influences [53]. The actual – so called „preventive“ – proceeding concerning mask obligations in many countries around the world and especially in schools appears not in line with the Helsinki Declaration [164], the Lisbon Declaration [165] and the Nuremberg Code [166].



## 5. Limitations

In this review we only focused on CO<sub>2</sub>, however, other noxious agents in the masks contribute to toxicological long-term effects like the inhalation of synthetic microfibers, carcinogenic compounds and volatile organic compounds could also play a role regarding our research question [167,168].

It must be remembered that the increased carbon dioxide content of the breathing air behind the mask may also lead to a displacement of oxygen. In this case, in addition to hypercapnia, hypoxia could also have an effect, which would certainly be very important for the teratogenic aspects (e.g. spinal malformations due to hypoxia) [169]. The fact that in this context (toxic effect of carbon dioxide versus hypoxia) no sharp distinction was made can lead up to the mixing of sequelae, which was mentioned by Hubert Meesen [170].

As this article is a scoping review and not a systematic one (with meta-analysis) we did not perform a mathematical evaluation with effect sizes to further quantify the phenomena of CO<sub>2</sub> accumulation during mask use.

The potential toxicological effects of carbon dioxide discussed here on early life are based on data from animal studies and their comparison with levels measured in humans using masks.

Measurements in humans using masks and in animal experiments with low-level carbon dioxide are reproducible, but population effects could not be further quantified beyond the available information because there are too few studies that examine the causal relationship between mask use and miscarriages, infertility, and neurodevelopmental disorders further. Because such human experiments are not ethically defensible, there is no human-experimental data to support our hypothesis of CO<sub>2</sub> toxicity to mask-wearing pregnant women, children, and adolescents.

## 6. Conclusions

A significant rise in carbon dioxide occurring while wearing a mask is scientifically proven in many studies [48,64–71,73,77–84,86–91], especially for N95-masks (Table 2) [66,69–71,73,77–80,82,84–86,88,90,91] due to their higher deadspace and breathing resistance [48].

Fresh air has around 0.04% CO<sub>2</sub> while masks bear a possible chronic exposure to low level carbon dioxide of 1.41 to 3.2% CO<sub>2</sub> of the inhaled air in reliable human experiments (Table 1) [64,65,69,71,73].

Animal experimental data shows deleterious proven effects of elevated CO<sub>2</sub> of inhaled air in the long term with threshold values of above 0.3%, 0.5% and 0.8% (Neuron destruction, impaired memory and learning, increased anxiety, destruction of cells in testes, stillbirth, and birth defects) [58,104,106–108,113,114]. The risk for children's mental development starts at levels of above 0.3% [108,113], to adolescent male sexual development at levels of above 0.5% [114], as well as to unborn life at levels of above 0.8 % [58,106,107] resulting in reduced cognitive performance, reduced fertility and stillbirths (Table 3).

There is circumstantial evidence that popular mask use may be related to current observations of a significant rise of 28% to 33% in stillbirths worldwide and a reduced verbal, motor, and overall cognitive performance of two full standard deviations in scores in children born during the pandemic [62,63,124–126,141]. According to the data found, wearing face masks also has the potential to exceed acute (3% CO<sub>2</sub> for 15 minutes) and chronic (0.5% CO<sub>2</sub> for 8 hours) NIOSH limits for CO<sub>2</sub> respiration. Even if these are not exceeded, assuming that time is a toxicological variable equivalent to dose (Haber's rule of inhalation toxicology, also known as  $c^n \times t^m = K$ ) [117–119] long term everyday mask use should be further examined, as chronic (repeated) exposure to smaller daily doses (even subliminally) may not differ significantly in its effect on the organism from exposure to

acute/occasional higher (threshold) doses [117,118]. Instead of only worrying about the potential risks of a future harmful long-term CO<sub>2</sub> increase in the atmosphere with impact on human health [112,171,172], the focus of research should also be on the current mask-related CO<sub>2</sub> increase in breathing air (Table 1) with its numerous effects. Face mask experiments with appropriately long (and variable) exposure times and measurements of e.g., electrolyte, acid-base and renal excretion haemostasis are needed to investigate toxicological risks of carbon dioxide rebreathing for the most vulnerable groups.

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## Literature

- [1] What Countries Require or Recommend Masks In Public?, #Masks4All. (2020). <https://masks4all.co/what-countries-require-masks-in-public/> (accessed November 7, 2021).
- [2] S.N. Ladhani, Face masking for children - time to reconsider, *Journal of Infection*. 85 (2022) 623–624. <https://doi.org/10.1016/j.jinf.2022.09.020>.
- [3] S. Thomson, Mask mandates for children during the COVID-19 pandemic: an international human rights perspective, *Scand J Public Health*. 50 (2022) 683–685. <https://doi.org/10.1177/14034948221081087>.

- [4] S. Schwarz, E. Jenetzky, H. Krafft, T. Maurer, D. Martin, Corona children studies “Co-Ki”: First results of a Germany-wide registry on mouth and nose covering (mask) in children, 2020. <https://doi.org/10.21203/rs.3.rs-124394/v1>.
- [5] Coronavirus disease (COVID-19): Children and masks, (n.d.). <https://www.who.int/news-room/questions-and-answers/item/q-a-children-and-masks-related-to-covid-19> (accessed December 28, 2022).
- [6] Face covering policies during the COVID-19 pandemic, Our World in Data. (n.d.). <https://ourworldindata.org/grapher/face-covering-policies-covid> (accessed December 29, 2022).
- [7] N.L. Belkin, The evolution of the surgical mask: filtering efficiency versus effectiveness, *Infect Control Hosp Epidemiol.* 18 (1997) 49–57. <https://doi.org/10.2307/30141964>.
- [8] C. Matuschek, F. Moll, H. Fangerau, J.C. Fischer, K. Zänker, M. van Griensven, M. Schneider, D. Kindgen-Milles, W.T. Knoefel, A. Lichtenberg, B. Tamaskovics, F.J. Djiepmo-Njanang, W. Budach, S. Corradini, D. Häussinger, T. Feldt, B. Jensen, R. Pelka, K. Orth, M. Peiper, O. Grebe, K. Maas, E. Bölke, J. Haussmann, The history and value of face masks, *European Journal of Medical Research.* 25 (2020) 23. <https://doi.org/10.1186/s40001-020-00423-4>.
- [9] S.-A. Lee, S.A. Grinshpun, T. Reponen, Respiratory Performance Offered by N95 Respirators and Surgical Masks: Human Subject Evaluation with NaCl Aerosol Representing Bacterial and Viral Particle Size Range, *Ann Occup Hyg.* 52 (2008) 177–185. <https://doi.org/10.1093/annhyg/men005>.
- [10] M. Vincent, P. Edwards, Disposable surgical face masks for preventing surgical wound infection in clean surgery, *Cochrane Database Syst Rev.* 4 (2016) CD002929. <https://doi.org/10.1002/14651858.CD002929.pub3>.
- [11] G. Leech, C. Rogers-Smith, J.T. Monrad, J.B. Sandbrink, B. Snodin, R. Zinkov, B. Rader, J.S. Brownstein, Y. Gal, S. Bhatt, M. Sharma, S. Mindermann, J.M. Brauner, L. Aitchison, Mask wearing in community settings reduces SARS-CoV-2 transmission, *Proc Natl Acad Sci U S A.* 119 (2022) e2119266119. <https://doi.org/10.1073/pnas.2119266119>.
- [12] Y. Cheng, N. Ma, C. Witt, S. Rapp, P.S. Wild, M.O. Andreae, U. Pöschl, H. Su, Face masks effectively limit the probability of SARS-CoV-2 transmission, *Science.* 372 (2021) 1439–1443. <https://doi.org/10.1126/science.abg6296>.
- [13] H. Ueki, Y. Furusawa, K. Iwatsuki-Horimoto, M. Imai, H. Kabata, H. Nishimura, Y. Kawaoka, Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2, *MSphere.* 5 (2020). <https://doi.org/10.1128/mSphere.00637-20>.
- [14] S. Asadi, C.D. Cappa, S. Barreda, A.S. Wexler, N.M. Bouvier, W.D. Ristenpart, Efficacy of masks and face coverings in controlling outward aerosol particle emission from expiratory activities, *Scientific Reports.* 10 (2020) 15665. <https://doi.org/10.1038/s41598-020-72798-7>.
- [15] A.A. Chughtai, S. Stelzer-Braid, W. Rawlinson, G. Pontivivo, Q. Wang, Y. Pan, D. Zhang, Y. Zhang, L. Li, C.R. MacIntyre, Contamination by respiratory viruses on outer surface of medical masks used by hospital healthcare workers, *BMC Infect Dis.* 19 (2019) 491. <https://doi.org/10.1186/s12879-019-4109-x>.
- [16] F. Drewnick, J. Pikmann, F. Fachinger, L. Moormann, F. Sprang, S. Borrmann, Aerosol filtration efficiency of household materials for homemade face masks: Influence of material properties, particle size, particle electrical charge, face velocity, and leaks, *Aerosol Science and Technology.* 55 (2021) 63–79. <https://doi.org/10.1080/02786826.2020.1817846>.

- [17] Y. Shah, J.W. Kurelek, S.D. Peterson, S. Yarusevych, Experimental investigation of indoor aerosol dispersion and accumulation in the context of COVID-19: Effects of masks and ventilation, *Physics of Fluids*. 33 (2021) 073315. <https://doi.org/10.1063/5.0057100>.
- [18] Y. Li, M. Liang, L. Gao, M. Ayaz Ahmed, J.P. Uy, C. Cheng, Q. Zhou, C. Sun, Face masks to prevent transmission of COVID-19: A systematic review and meta-analysis, *Am J Infect Control*. 49 (2021) 900–906. <https://doi.org/10.1016/j.ajic.2020.12.007>.
- [19] J. Howard, A. Huang, Z. Li, Z. Tufekci, V. Zdimal, H.-M. van der Westhuizen, A. von Delft, A. Price, L. Fridman, L.-H. Tang, V. Tang, G.L. Watson, C.E. Bax, R. Shaikh, F. Questier, D. Hernandez, L.F. Chu, C.M. Ramirez, A.W. Rimoin, An evidence review of face masks against COVID-19, *PNAS*. 118 (2021). <https://doi.org/10.1073/pnas.2014564118>.
- [20] T. Jefferson, M. Jones, L.A.A. Ansari, G. Bawazeer, E. Beller, J. Clark, J. Conly, C.D. Mar, E. Dooley, E. Ferroni, P. Glasziou, T. Hoffman, S. Thorning, M.V. Driel, Physical interventions to interrupt or reduce the spread of respiratory viruses. Part 1 - Face masks, eye protection and person distancing: systematic review and meta-analysis, *MedRxiv*. (2020) 2020.03.30.20047217. <https://doi.org/10.1101/2020.03.30.20047217>.
- [21] T. Jefferson, L. Dooley, E. Ferroni, L.A. Al-Ansary, M.L. van Driel, G.A. Bawazeer, M.A. Jones, T.C. Hoffmann, J. Clark, E.M. Beller, P.P. Glasziou, J.M. Conly, Physical interventions to interrupt or reduce the spread of respiratory viruses, *Cochrane Database of Systematic Reviews*. (2023). <https://doi.org/10.1002/14651858.CD006207.pub6>.
- [22] J. Xiao, E.Y.C. Shiu, H. Gao, J.Y. Wong, M.W. Fong, S. Ryu, B.J. Cowling, Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Personal Protective and Environmental Measures - Volume 26, Number 5—May 2020 - *Emerging Infectious Diseases journal - CDC*, (n.d.). <https://doi.org/10.3201/eid2605.190994>.
- [23] M.X. Wang, S.X.W. Gwee, P.E.Y. Chua, J. Pang, Effectiveness of Surgical Face Masks in Reducing Acute Respiratory Infections in Non-Healthcare Settings: A Systematic Review and Meta-Analysis, *Frontiers in Medicine*. 7 (2020). <https://www.frontiersin.org/articles/10.3389/fmed.2020.564280> (accessed November 26, 2022).
- [24] M.S. Fønhus, T.K. Dalsbø, K.G. Brurberg, Facemasks to prevent transmission of respiratory illness, such as COVID-19, *Norwegian Institute of Public Health*, 2021. <https://fhi.brage.unit.no/fhi-xmlui/handle/11250/2756758> (accessed November 7, 2021).
- [25] J.C. Jakobsen, C. Gluud, The Necessity of Randomized Clinical Trials, *Journal of Advances in Medicine and Medical Research*. (2013) 1453–1468. <https://doi.org/10.9734/BJMMR/2013/3208>.
- [26] M.L. Meldrum, A BRIEF HISTORY OF THE RANDOMIZED CONTROLLED TRIAL: From Oranges and Lemons to the Gold Standard, *Hematology/Oncology Clinics of North America*. 14 (2000) 745–760. [https://doi.org/10.1016/S0889-8588\(05\)70309-9](https://doi.org/10.1016/S0889-8588(05)70309-9).
- [27] A.E. Aiello, V. Perez, R.M. Coulborn, B.M. Davis, M. Uddin, A.S. Monto, Facemasks, hand hygiene, and influenza among young adults: a randomized intervention trial, *PLoS One*. 7 (2012) e29744. <https://doi.org/10.1371/journal.pone.0029744>.
- [28] A.E. Aiello, G.F. Murray, V. Perez, R.M. Coulborn, B.M. Davis, M. Uddin, D.K. Shay, S.H. Waterman, A.S. Monto, Mask use, hand hygiene, and seasonal influenza-like illness among young adults: a randomized intervention trial, *J Infect Dis*. 201 (2010) 491–498. <https://doi.org/10.1086/650396>.

- [29] E. Zain Alabdeen, A. Choudhry, D. Al-Naji, Effect of use of Face mask on Hajj related Acute Respiratory Infection among Hajjis from Riyadh -A Health Promotion Intervention study, *FETP Saudi Epidemiology Bulletin*. 12 (2005) 27–28.
- [30] O. Barasheed, N. Almasri, A.-M. Badahdah, L. Heron, J. Taylor, K. McPhee, I. Ridda, E. Haworth, D.E. Dwyer, H. Rashid, R. Booy, Hajj Research Team, Pilot Randomised Controlled Trial to Test Effectiveness of Facemasks in Preventing Influenza-like Illness Transmission among Australian Hajj Pilgrims in 2011, *Infect Disord Drug Targets*. 14 (2014) 110–116. <https://doi.org/10.2174/1871526514666141021112855>.
- [31] M. Alfelali, E.A. Haworth, O. Barasheed, A.-M. Badahdah, H. Bokhary, M. Tashani, M.I. Azeem, J. Kok, J. Taylor, E.H. Barnes, H. El Bashir, G. Khandaker, E.C. Holmes, D.E. Dwyer, L.G. Heron, G.J. Wilson, R. Booy, H. Rashid, Hajj Research Team, Facemask against viral respiratory infections among Hajj pilgrims: A challenging cluster-randomized trial, *PLoS One*. 15 (2020) e0240287. <https://doi.org/10.1371/journal.pone.0240287>.
- [32] L. Canini, L. Andréoletti, P. Ferrari, R. D'Angelo, T. Blanchon, M. Lemaitre, L. Filleul, J.-P. Ferry, M. Desmaizieres, S. Smadja, A.-J. Valleron, F. Carrat, Surgical mask to prevent influenza transmission in households: a cluster randomized trial, *PLoS One*. 5 (2010) e13998. <https://doi.org/10.1371/journal.pone.0013998>.
- [33] C.R. MacIntyre, S. Cauchemez, D.E. Dwyer, H. Seale, P. Cheung, G. Browne, M. Fasher, J. Wood, Z. Gao, R. Booy, N. Ferguson, Face mask use and control of respiratory virus transmission in households, *Emerg Infect Dis*. 15 (2009) 233–241. <https://doi.org/10.3201/eid1502.081167>.
- [34] C.R. MacIntyre, Y. Zhang, A.A. Chughtai, H. Seale, D. Zhang, Y. Chu, H. Zhang, B. Rahman, Q. Wang, Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness, *BMJ Open*. 6 (2016) e012330. <https://doi.org/10.1136/bmjopen-2016-012330>.
- [35] J.M. Simmerman, P. Suntarattiwong, J. Levy, R.G. Jarman, S. Kaewchana, R.V. Gibbons, B.J. Cowling, W. Sanasuttipun, S.A. Maloney, T.M. Uyeki, L. Kamimoto, T. Chotipitayasunondh, Findings from a household randomized controlled trial of hand washing and face masks to reduce influenza transmission in Bangkok, Thailand, *Influenza Other Respir Viruses*. 5 (2011) 256–267. <https://doi.org/10.1111/j.1750-2659.2011.00205.x>.
- [36] B.J. Cowling, R.O.P. Fung, C.K.Y. Cheng, V.J. Fang, K.H. Chan, W.H. Seto, R. Yung, B. Chiu, P. Lee, T.M. Uyeki, P.M. Houck, J.S.M. Peiris, G.M. Leung, Preliminary Findings of a Randomized Trial of Non-Pharmaceutical Interventions to Prevent Influenza Transmission in Households, *PLoS One*. 3 (2008). <https://doi.org/10.1371/journal.pone.0002101>.
- [37] B.J. Cowling, K.-H. Chan, V.J. Fang, C.K.Y. Cheng, R.O.P. Fung, W. Wai, J. Sin, W.H. Seto, R. Yung, D.W.S. Chu, B.C.F. Chiu, P.W.Y. Lee, M.C. Chiu, H.C. Lee, T.M. Uyeki, P.M. Houck, J.S.M. Peiris, G.M. Leung, Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial, *Ann Intern Med*. 151 (2009) 437–446. <https://doi.org/10.7326/0003-4819-151-7-200910060-00142>.
- [38] T. Suess, C. Remschmidt, S.B. Schink, B. Schweiger, A. Nitsche, K. Schroeder, J. Doellinger, J. Milde, W. Haas, I. Koehler, G. Krause, U. Buchholz, The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009-2011, *BMC Infect Dis*. 12 (2012) 26. <https://doi.org/10.1186/1471-2334-12-26>.

- [39] E.L. Larson, Y. Ferng, J. Wong-McLoughlin, S. Wang, M. Haber, S.S. Morse, Impact of Non-Pharmaceutical Interventions on URIs and Influenza in Crowded, Urban Households, *Public Health Rep.* 125 (2010) 178–191.
- [40] J.L. Jacobs, S. Ohde, O. Takahashi, Y. Tokuda, F. Omata, T. Fukui, Use of surgical face masks to reduce the incidence of the common cold among health care workers in Japan: a randomized controlled trial, *Am J Infect Control.* 37 (2009) 417–419. <https://doi.org/10.1016/j.ajic.2008.11.002>.
- [41] H. Bundgaard, J.S. Bundgaard, D.E.T. Raaschou-Pedersen, C. von Buchwald, T. Todsén, J.B. Norsk, M.M. Pries-Heje, C.R. Vissing, P.B. Nielsen, U.C. Winsløw, K. Fogh, R. Hasselbalch, J.H. Kristensen, A. Ringgaard, M. Porsborg Andersen, N.B. Goecke, R. Trebbien, K. Skovgaard, T. Benfield, H. Ullum, C. Torp-Pedersen, K. Iversen, Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers, *Ann Intern Med.* (2020). <https://doi.org/10.7326/M20-6817>.
- [42] J. Abaluck, L.H. Kwong, A. Styczynski, A. Haque, Md.A. Kabir, E. Bates-Jefferys, E. Crawford, J. Benjamin-Chung, S. Raihan, S. Rahman, S. Benhachmi, N.Z. Bintee, P.J. Winch, M. Hossain, H.M. Reza, A.A. Jaber, S.G. Momen, A. Rahman, F.L. Banti, T.S. Huq, S.P. Luby, A.M. Mobarak, Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh, *Science.* 375 (2021) eabi9069. <https://doi.org/10.1126/science.abi9069>.
- [43] 2021-09-20 Do Face Masks Reduce COVID-19 Spread in Bangladesh Are the Abaluck et al Results Reliable - Denis Rancourt, (n.d.). [https://denisrancourt.ca/entries.php?id=106&name=2021\\_09\\_20\\_do\\_face\\_masks\\_reduce\\_covid\\_19\\_spread\\_in\\_bangladesh\\_are\\_the\\_abaluck\\_et\\_al\\_results\\_reliable](https://denisrancourt.ca/entries.php?id=106&name=2021_09_20_do_face_masks_reduce_covid_19_spread_in_bangladesh_are_the_abaluck_et_al_results_reliable) (accessed December 29, 2022).
- [44] C.J. Heneghan, E.A. Spencer, J. Brassey, A. Plüddemann, I.J. Onakpoya, D.H. Evans, J.M. Conly, T. Jefferson, SARS-CoV-2 and the role of orofecal transmission: a systematic review, (2021). <https://doi.org/10.12688/f1000research.51592.2>.
- [45] A. Boretti, Efficacy of Generalized Face Masking Mandates, *Health Services Research and Managerial Epidemiology.* 8 (2021) 23333928211058024. <https://doi.org/10.1177/23333928211058023>.
- [46] E. Coma, M. Català, L. Méndez-Boo, S. Alonso, E. Hermsilla, E. Alvarez-Lacalle, D. Pino, M. Medina, L. Asso, A. Gatell, Q. Bassat, A. Mas, A. Soriano-Arandes, F.F. Avilés, C. Prats, Unravelling the role of the mandatory use of face covering masks for the control of SARS-CoV-2 in schools: a quasi-experimental study nested in a population-based cohort in Catalonia (Spain), *Archives of Disease in Childhood.* (2022). <https://doi.org/10.1136/archdischild-2022-324172>.
- [47] S. Mader, T. Rüttenauer, The Effects of Non-pharmaceutical Interventions on COVID-19 Mortality: A Generalized Synthetic Control Approach Across 169 Countries, *Frontiers in Public Health.* 10 (2022). <https://www.frontiersin.org/articles/10.3389/fpubh.2022.820642> (accessed November 28, 2022).
- [48] K. Kisielinski, P. Giboni, A. Prescher, B. Klosterhalfen, D. Graessel, S. Funken, O. Kempfski, O. Hirsch, Is a Mask That Covers the Mouth and Nose Free from Undesirable Side Effects in Everyday Use and Free of Potential Hazards?, *International Journal of Environmental Research and Public Health.* 18 (2021) 4344. <https://doi.org/10.3390/ijerph18084344>.



- [49] I. Kappstein, Mund-Nasen-Schutz in der Öffentlichkeit: Keine Hinweise für eine Wirksamkeit, *Krankenhaushygiene* up2date. 15 (2020) 279–295. <https://doi.org/10.1055/a-1174-6591>.
- [50] J. Gralton, M.-L. McLaws, Protecting healthcare workers from pandemic influenza: N95 or surgical masks?, *Crit Care Med.* 38 (2010) 657–667. <https://doi.org/10.1097/ccm.0b013e3181b9e8b3>.
- [51] S.E. Budzyn, M.J. Panaggio, S.E. Parks, M. Papazian, J. Magid, M. Eng, L.C. Barrios, Pediatric COVID-19 Cases in Counties With and Without School Mask Requirements - United States, July 1-September 4, 2021, *MMWR Morb Mortal Wkly Rep.* 70 (2021) 1377–1378. <https://doi.org/10.15585/mmwr.mm7039e3>.
- [52] A. Chandra, T.B. Høeg, Lack of correlation between school mask mandates and paediatric COVID-19 cases in a large cohort, *Journal of Infection.* 85 (2022) 671–675. <https://doi.org/10.1016/j.jinf.2022.09.019>.
- [53] E.M. Faustman, S.M. Silbernagel, R.A. Fenske, T.M. Burbacher, R.A. Ponce, Mechanisms underlying Children’s susceptibility to environmental toxicants, *Environ Health Perspect.* 108 Suppl 1 (2000) 13–21. <https://doi.org/10.1289/ehp.00108s113>.
- [54] N.R. Smart, C.J. Horwell, T.S. Smart, K.S. Galea, Assessment of the Wearability of Facemasks against Air Pollution in Primary School-Aged Children in London, *International Journal of Environmental Research and Public Health.* 17 (2020) 3935. <https://doi.org/10.3390/ijerph17113935>.
- [55] K. Azuma, N. Kagi, U. Yanagi, H. Osawa, Effects of low-level inhalation exposure to carbon dioxide in indoor environments: A short review on human health and psychomotor performance, *Environment International.* 121 (2018) 51–56. <https://doi.org/10.1016/j.envint.2018.08.059>.
- [56] A. Guais, G. Brand, L. Jacquot, M. Karrer, S. Dukan, G. Grévillet, T.J. Molina, J. Bonte, M. Regnier, L. Schwartz, Toxicity of Carbon Dioxide: A Review, *Chem. Res. Toxicol.* 24 (2011) 2061–2070. <https://doi.org/10.1021/tx200220r>.
- [57] CDC - NIOSH Pocket Guide to Chemical Hazards - Carbon dioxide, (n.d.). <https://www.cdc.gov/niosh/npg/npgd0103.html> (accessed January 1, 2023).
- [58] W.R. Howard, B. Wong, M. Okolica, K.S. Bynum, R.A. James, The Prenatal Development Effects of Carbon Dioxide (CO<sub>2</sub>) Exposure in Rats (*Rattus Norvegicus*):, Defense Technical Information Center, Fort Belvoir, VA, 2012. <https://doi.org/10.21236/ADA583166>.
- [59] X. Huang, J. Lin, D. Demner-Fushman, Evaluation of PICO as a knowledge representation for clinical questions, *AMIA Annu Symp Proc.* (2006) 359–363.
- [60] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C.J. Cates, H.-Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernán, S. Hopewell, A. Hróbjartsson, D.R. Junqueira, P. Jüni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I.R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, *BMJ.* 366 (2019) 14898. <https://doi.org/10.1136/bmj.l4898>.
- [61] casp, Home, CASP - Critical Appraisal Skills Programme. (n.d.). <https://casp-uk.net/> (accessed September 24, 2022).
- [62] B. Chmielewska, I. Barratt, R. Townsend, E. Kalafat, J. van der Meulen, I. Gurol-Urganci, P. O’Brien, E. Morris, T. Draycott, S. Thangaratinam, K.L. Doare, S. Ladhani, P. von Dadelszen,

- L. Magee, A. Khalil, Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis, *The Lancet Global Health*. 0 (2021).  
[https://doi.org/10.1016/S2214-109X\(21\)00079-6](https://doi.org/10.1016/S2214-109X(21)00079-6).
- [63] C. Vaccaro, F. Mahmoud, L. Aboulatta, B. Aloud, S. Eltonsy, The impact of COVID-19 first wave national lockdowns on perinatal outcomes: a rapid review and meta-analysis, *BMC Pregnancy and Childbirth*. 21 (2021) 676. <https://doi.org/10.1186/s12884-021-04156-y>.
- [64] U. Butz, Rückatmung von Kohlendioxid bei Verwendung von Operationsmasken als hygienischer Mundschutz an medizinischem Fachpersonal, *Universitätsbibliothek der Technischen Universität München*, 2005.
- [65] F. Pifarré, D.D. Zabala, G. Grazioli, I. de Yzaguirre i Maura, COVID 19 and mask in sports, *Apunts Sports Medicine*. (2020). <https://doi.org/10.1016/j.apunsm.2020.06.002>.
- [66] T. Blad, J. Nijssen, F. Broeren, B. Boogaard, S. Lampaert, S. van den Toorn, J. van den Dobbelen, A Rapidly Deployable Test Suite for Respiratory Protective Devices in the COVID-19 Pandemic, *Applied Biosafety*. 25 (2020) 161–168.  
<https://doi.org/10.1177/1535676020947284>.
- [67] H. Salati, M. Khamooshi, S. Vahaji, F.C. Christo, D.F. Fletcher, K. Inthavong, N95 respirator mask breathing leads to excessive carbon dioxide inhalation and reduced heat transfer in a human nasal cavity, *Phys Fluids* (1994). 33 (2021) 081913. <https://doi.org/10.1063/5.0061574>.
- [68] X. Zhang, H. Li, S. Shen, M. Cai, Investigation of the flow-field in the upper respiratory system when wearing N95 filtering facepiece respirator, *J Occup Environ Hyg*. 13 (2016) 372–382.  
<https://doi.org/10.1080/15459624.2015.1116697>.
- [69] E.J. Sinkule, J.B. Powell, F.L. Goss, Evaluation of N95 respirator use with a surgical mask cover: effects on breathing resistance and inhaled carbon dioxide, *Ann Occup Hyg*. 57 (2013) 384–398. <https://doi.org/10.1093/annhyg/mes068>.
- [70] E.A. Laferty, R.T. McKay, Physiologic effects and measurement of carbon dioxide and oxygen levels during qualitative respirator fit testing, *J. Chem. Health Saf*. 13 (2006) 22–28.  
<https://doi.org/10.1016/j.jchas.2005.11.015>.
- [71] R.J. Roberge, A. Coca, W.J. Williams, J.B. Powell, A.J. Palmiero, Physiological impact of the N95 filtering facepiece respirator on healthcare workers, *Respir Care*. 55 (2010) 569–577.
- [72] J. Otmar Geiss, Effect of Wearing Face Masks on the Carbon Dioxide Concentration in the Breathing Zone, *Aerosol Air Qual. Res*. 20 (2020). <https://doi.org/10.4209/aaqr.2020.07.0403>.
- [73] M.S.M. Rhee, C.D. Lindquist, M.T. Silvestrini, A.C. Chan, J.J.Y. Ong, V.K. Sharma, Carbon dioxide increases with face masks but remains below short-term NIOSH limits, *BMC Infect Dis*. 21 (2021) 354. <https://doi.org/10.1186/s12879-021-06056-0>.
- [74] I. Ellingsen, G. Sydnæs, A. Hauge, J.-A. Zwart, K. Liestøl, G. Nicolaysen, CO<sub>2</sub> sensitivity in humans breathing 1 or 2% CO<sub>2</sub> in air, *Acta Physiologica Scandinavica*. 129 (1987) 195–202.  
<https://doi.org/10.1111/j.1748-1716.1987.tb08059.x>.
- [75] K.E. Schaefer, Respiratory adaptation to chronic hypercapnia, *Ann N Y Acad Sci*. 109 (1963) 772–782. <https://doi.org/10.1111/j.1749-6632.1963.tb13505.x>.
- [76] R. Fantin, The effect of wearing an FFP3 mask (3M TM Aura TM ) with an exhalation valve on gas exchange in medical staff, *Int J Occup Med Environ Health*. (2021).  
<https://doi.org/10.13075/ijomeh.1896.01809>.

- [77] C. Bharatendu, J.J.Y. Ong, Y. Goh, B.Y.Q. Tan, A.C.Y. Chan, J.Z.Y. Tang, A.S. Leow, A. Chin, K.W.X. Sooi, Y.L. Tan, C.S. Hong, B.Z. Chin, E. Ng, T.W. Foong, H.L. Teoh, S.T. Ong, P. Lee, D. Khoo, G. Tsvigoulis, A.V. Alexandrov, V.K. Sharma, Powered Air Purifying Respirator (PAPR) restores the N95 face mask induced cerebral hemodynamic alterations among Healthcare Workers during COVID-19 Outbreak, *J Neurol Sci.* 417 (2020) 117078. <https://doi.org/10.1016/j.jns.2020.117078>.
- [78] D. Epstein, A. Korytny, Y. Isenberg, E. Marcusohn, R. Zukermann, B. Bishop, S. Minha, A. Raz, A. Miller, Return to training in the COVID-19 era: The physiological effects of face masks during exercise, *Scandinavian Journal of Medicine & Science in Sports.* n/a (2020). <https://doi.org/10.1111/sms.13832>.
- [79] D.Ä.G. Georgi C, Haase-Fielitz A, Meretz D, Gäsert L, Butter C Redaktion Deutsches, The impact of commonly-worn face masks on physiological parameters and on discomfort during standard work-related physical effort (02.10.2020), *Deutsches Ärzteblatt.* (n.d.). <https://www.aerzteblatt.de/int/archive/article?id=215616> (accessed November 9, 2020).
- [80] S.Y. Kyung, Y. Kim, H. Hwang, J.-W. Park, S.H. Jeong, Risks of N95 Face Mask Use in Subjects With COPD, *Respir Care.* 65 (2020) 658–664. <https://doi.org/10.4187/respcare.06713>.
- [81] Y. Mo, Risk and impact of using mask on COPD patients with acute exacerbation during the COVID-19 outbreak: a retrospective study, (2020). <https://doi.org/10.21203/rs.3.rs-39747/v1>.
- [82] T. Rebmann, R. Carrico, J. Wang, Physiologic and other effects and compliance with long-term respirator use among medical intensive care unit nurses, *Am J Infect Control.* 41 (2013) 1218–1223. <https://doi.org/10.1016/j.ajic.2013.02.017>.
- [83] R.J. Roberge, J.-H. Kim, S.M. Benson, Absence of consequential changes in physiological, thermal and subjective responses from wearing a surgical mask, *Respiratory Physiology & Neurobiology.* 181 (2012) 29–35. <https://doi.org/10.1016/j.resp.2012.01.010>.
- [84] R.J. Roberge, J.-H. Kim, J.B. Powell, N95 respirator use during advanced pregnancy, *Am J Infect Control.* 42 (2014) 1097–1100. <https://doi.org/10.1016/j.ajic.2014.06.025>.
- [85] P.S.Y. Tong, A.S. Kale, K. Ng, A.P. Loke, M.A. Choolani, C.L. Lim, Y.H. Chan, Y.S. Chong, P.A. Tambyah, E.-L. Yong, Respiratory consequences of N95-type Mask usage in pregnant healthcare workers—a controlled clinical study, *Antimicrobial Resistance & Infection Control.* 4 (2015) 48. <https://doi.org/10.1186/s13756-015-0086-z>.
- [86] R. Lubrano, S. Bloise, A. Marcellino, C.P. Ciolli, A. Testa, E. De Luca, A. Dilillo, S. Mallardo, S. Isoldi, V. Martucci, M. Sanseviero, E. Del Giudice, C. Malvaso, C. Iacovelli, R. Leone, D. Iorfida, F. Ventriglia, Effects of N95 Mask Use on Pulmonary Function in Children, *J Pediatr.* 237 (2021) 143–147. <https://doi.org/10.1016/j.jpeds.2021.05.050>.
- [87] G. Zhang, M. Li, M. Zheng, X. Cai, J. Yang, S. Zhang, A. Yilifate, Y. Zheng, Q. Lin, J. Liang, L. Guo, H. Ou, Effect of Surgical Masks on Cardiopulmonary Function in Healthy Young Subjects: A Crossover Study, *Front Physiol.* 12 (2021) 710573. <https://doi.org/10.3389/fphys.2021.710573>.
- [88] M. Mapelli, E. Salvioni, F.D. Martino, I. Mattavelli, P. Gugliandolo, C. Vignati, S. Farina, P. Palermo, J. Campodonico, R. Maragna, G.L. Russo, A. Bonomi, S. Sciomer, P. Agostoni, “You can leave your mask on”: effects on cardiopulmonary parameters of different airway protection masks at rest and during maximal exercise, *European Respiratory Journal.* (2021). <https://doi.org/10.1183/13993003.04473-2020>.

- [89] H. Dirol, E. Alkan, M. Sindel, T. Ozdemir, D. Erbas, The physiological and disturbing effects of surgical face masks in the COVID-19 era, *BLL*. 122 (2021) 821–825. [https://doi.org/10.4149/BLL\\_2021\\_131](https://doi.org/10.4149/BLL_2021_131).
- [90] J.-H. Kim, S.M. Benson, R.J. Roberge, Pulmonary and heart rate responses to wearing N95 filtering facepiece respirators, *Am J Infect Control*. 41 (2013) 24–27. <https://doi.org/10.1016/j.ajic.2012.02.037>.
- [91] P. Sukul, J. Bartels, P. Fuchs, P. Trefz, R. Remy, L. Rührmund, S. Kamysek, J.K. Schubert, W. Miekisch, Effects of COVID-19 protective face masks and wearing durations on respiratory haemodynamic physiology and exhaled breath constituents, *European Respiratory Journal*. 60 (2022). <https://doi.org/10.1183/13993003.00009-2022>.
- [92] S.L. Shein, S. Whitticar, K.K. Mascho, E. Pace, R. Speicher, K. Deakins, The effects of wearing facemasks on oxygenation and ventilation at rest and during physical activity, *PLoS One*. 16 (2021) e0247414. <https://doi.org/10.1371/journal.pone.0247414>.
- [93] E. Jafari, M. Togha, H. Kazemizadeh, S. Haghighi, S. Nasergivehchi, M. Saatchi, S. Ariyanfar, Evaluation of headache associated with personal protective equipment during COVID-19, *Brain and Behavior*. n/a (n.d.) e2435. <https://doi.org/10.1002/brb3.2435>.
- [94] C.J. Doherty, L.M. Mann, S.A. Angus, J.S. Chan, Y. Molgat-Seon, P.B. Dominelli, Impact of wearing a surgical and cloth mask during cycle exercise, *Appl Physiol Nutr Metab*. 46 (2021) 753–762. <https://doi.org/10.1139/apnm-2021-0190>.
- [95] R. Lubrano, S. Bloise, A. Testa, A. Marcellino, A. Dilillo, S. Mallardo, S. Isoldi, V. Martucci, M. Sanseviero, E. Del Giudice, C. Malvaso, D. Iorfida, F. Ventriglia, Assessment of Respiratory Function in Infants and Young Children Wearing Face Masks During the COVID-19 Pandemic, *JAMA Netw Open*. 4 (2021) e210414. <https://doi.org/10.1001/jamanetworkopen.2021.0414>.
- [96] J.-H. Kim, T. Wu, J.B. Powell, R.J. Roberge, Physiologic and fit factor profiles of N95 and P100 filtering facepiece respirators for use in hot, humid environments, *Am J Infect Control*. 44 (2016) 194–198. <https://doi.org/10.1016/j.ajic.2015.08.027>.
- [97] K. Górska, P. Korczyński, M. Maskey-Warzęchowska, R. Chazan, R. Krenke, Variability of Transcutaneous Oxygen and Carbon Dioxide Pressure Measurements Associated with Sensor Location, *Adv Exp Med Biol*. 858 (2015) 39–46. [https://doi.org/10.1007/5584\\_2015\\_126](https://doi.org/10.1007/5584_2015_126).
- [98] E. Razi, G.A. Moosavi, K. Omidi, A. Khakpour Saebi, A. Razi, Correlation of end-tidal carbon dioxide with arterial carbon dioxide in mechanically ventilated patients, *Arch Trauma Res*. 1 (2012) 58–62. <https://doi.org/10.5812/atr.6444>.
- [99] M. Contini, A. Angelucci, A. Aliverti, P. Gugliandolo, B. Pezzuto, G. Berna, S. Romani, C.C. Tedesco, P. Agostoni, Comparison between PtCO<sub>2</sub> and PaCO<sub>2</sub> and Derived Parameters in Heart Failure Patients during Exercise: A Preliminary Study, *Sensors*. 21 (2021) 6666. <https://doi.org/10.3390/s21196666>.
- [100] N.J. Langford, Carbon Dioxide Poisoning, *Toxicol Rev*. 24 (2005) 229–235. <https://doi.org/10.2165/00139709-200524040-00003>.
- [101] K.E. Schaefer, S.M. Pasquale, A.A. Messier, H. Niemoeller, CO<sub>2</sub>-induced kidney calcification, *Undersea Biomed Res*. 6 Suppl (1979) S143-153.
- [102] M.M. Adeva-Andany, C. Fernández-Fernández, R. Sánchez-Bello, C. Donapetry-García, J. Martínez-Rodríguez, The role of carbonic anhydrase in the pathogenesis of vascular

- calcification in humans, *Atherosclerosis*. 241 (2015) 183–191. <https://doi.org/10.1016/j.atherosclerosis.2015.05.012>.
- [103] S.I. Tan, Y.L. Han, Y.J. Yu, C.Y. Chiu, Y.K. Chang, S. Ouyang, K.C. Fan, K.H. Lo, I.S. Ng, Efficient carbon dioxide sequestration by using recombinant carbonic anhydrase, *Process Biochemistry*. 73 (2018) 38–46. <https://doi.org/10.1016/j.procbio.2018.08.017>.
- [104] K.E. Schaefer, W.H. Douglas, A.A. Messier, M.L. Shea, P.A. Gohman, Effect of prolonged exposure to 0.5% CO<sub>2</sub> on kidney calcification and ultrastructure of lungs, *Undersea Biomed Res*. 6 Suppl (1979) S155-161.
- [105] W. Wirth, C. Gloxhuber, *Toxikologie*, in: 3rd ed., Georg Thieme Stuttgart New York, 1981: p. 156.
- [106] Evaluation of the Health Aspects of Carbon Dioxide as a Food Ingredient., Federation of American Societies for Experimental Biology, Bethesda, MD. Life Sciences Research Office.; Food and Drug Administration, Washington, DC. Bureau of Foods., 1979. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB80104615.xhtml> (accessed November 7, 2021).
- [107] W.R. Howard, B. Wong, K.S.B. Yeager, D.G. Stump, T. Edwards, R. Arden James, M.R. Goodwin, M.L. Gargas, Submarine exposure guideline recommendations for carbon dioxide based on the prenatal developmental effects of exposure in rats, *Birth Defects Res*. 111 (2019) 26–33. <https://doi.org/10.1002/bdr2.1417>.
- [108] M. Kiray, A.R. Sisman, U.M. Camsari, M. Evren, A. Dayi, B. Baykara, I. Aksu, M. Ates, N. Uysal, Effects of carbon dioxide exposure on early brain development in rats, *Biotechnic & Histochemistry*. 89 (2014) 371–383. <https://doi.org/10.3109/10520295.2013.872298>.
- [109] A. Veselá, J. Wilhelm, The role of carbon dioxide in free radical reactions of the organism, *Physiol Res*. 51 (2002) 335–339.
- [110] V.J. Forrest, Y.H. Kang, D.E. McClain, D.H. Robinson, N. Ramakrishnan, Oxidative stress-induced apoptosis prevented by Trolox, *Free Radic Biol Med*. 16 (1994) 675–684. [https://doi.org/10.1016/0891-5849\(94\)90182-1](https://doi.org/10.1016/0891-5849(94)90182-1).
- [111] J. Leon, D. Acuña-Castroviejo, R.M. Sainz, J.C. Mayo, D.-X. Tan, R.J. Reiter, Melatonin and mitochondrial function, *Life Sci*. 75 (2004) 765–790. <https://doi.org/10.1016/j.lfs.2004.03.003>.
- [112] T.A. Jacobson, J.S. Kler, M.T. Hernke, R.K. Braun, K.C. Meyer, W.E. Funk, Direct human health risks of increased atmospheric carbon dioxide, *Nat Sustain*. 2 (2019) 691–701. <https://doi.org/10.1038/s41893-019-0323-1>.
- [113] N. Uysal, M. Kiray, A.R. Sisman, B. Baykara, I. Aksu, A. Dayi, C. Gencoglu, M. Evren, E. Buyuk, F. Cetin, O. Acikgoz, Effects of exercise and poor indoor air quality on learning, memory and blood IGF-1 in adolescent mice, *Biotechnic & Histochemistry*. 89 (2014) 126–135. <https://doi.org/10.3109/10520295.2013.825318>.
- [114] N.L. Vandemark, B.D. Schanbacher, W.R. Gomes, Alterations in testes of rats exposed to elevated atmospheric carbon dioxide, *J Reprod Fertil*. 28 (1972) 457–459. <https://doi.org/10.1530/jrf.0.0280457>.
- [115] National Research Council, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*, The National Academies Press, Washington, DC, 2001. <https://doi.org/10.17226/10122>.

- [116] Safety Data Sheets, Linde Industrial Gases. (n.d.).  
[http://www.gas.linde.co.th/en/sheq/product\\_and\\_process\\_safety\\_information/safety\\_data\\_sheets/index.html](http://www.gas.linde.co.th/en/sheq/product_and_process_safety_information/safety_data_sheets/index.html) (accessed May 13, 2021).
- [117] K.K. Rozman, The role of time in toxicology or Haber's c×t product, *Toxicology*. 149 (2000) 35–42. [https://doi.org/10.1016/S0300-483X\(00\)00230-4](https://doi.org/10.1016/S0300-483X(00)00230-4).
- [118] K.K. Rozman, J. Doull, Dose and time as variables of toxicity, *Toxicology*. 144 (2000) 169–178. [https://doi.org/10.1016/S0300-483X\(99\)00204-8](https://doi.org/10.1016/S0300-483X(99)00204-8).
- [119] N.J. Bunce, R.B.J. Remillard, Haber's Rule: The Search for Quantitative Relationships in Toxicology, *Human and Ecological Risk Assessment: An International Journal*. 9 (2003) 973–985. <https://doi.org/10.1080/713610018>.
- [120] J.J. Knapik, M.A. Sharp, S. Darakjy, S.B. Jones, K.G. Hauret, B.H. Jones, Temporal Changes in the Physical Fitness of US Army Recruits, *Sports Med*. 36 (2006) 613–634.  
<https://doi.org/10.2165/00007256-200636070-00005>.
- [121] J. Knapik, The Army Physical Fitness Test (APFT): a review of the literature, *Mil Med*. 154 (1989) 326–329.
- [122] V.J. Flaherman, Y. Afshar, W.J. Boscardin, R.L. Keller, A. H Mardy, M.K. Prahll, C. T Phillips, I.V. Asiodu, V. Berghella, B.D. Chambers, J. Crear-Perry, D.J. Jamieson, V.L. Jacoby, S.L. Gaw, Infant Outcomes Following Maternal Infection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): First Report From the Pregnancy Coronavirus Outcomes Registry (PRIORITY) Study, *Clinical Infectious Diseases*. (2020).  
<https://doi.org/10.1093/cid/ciaa1411>.
- [123] C.L. DeSisto, Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization — United States, March 2020–September 2021, *MMWR Morb Mortal Wkly Rep*. 70 (2021). <https://doi.org/10.15585/mmwr.mm7047e1>.
- [124] L. Hui, M.B. Marzan, S. Potenza, D.L. Rolnik, N. Pritchard, J.M. Said, K.R. Palmer, C.L. Whitehead, P.M. Sheehan, J. Ford, B.W. Mol, S.P. Walker, Increase in preterm stillbirths and reduction in iatrogenic preterm births for fetal compromise: a multi-centre cohort study of COVID-19 lockdown effects in Melbourne, Australia, 2021.  
<https://doi.org/10.1101/2021.10.04.21264500>.
- [125] E.L. Rangel, M. Castillo-Angeles, S.R. Easter, R.B. Atkinson, A. Gosain, Y.-Y. Hu, Z. Cooper, T. Dey, E. Kim, Incidence of Infertility and Pregnancy Complications in US Female Surgeons, *JAMA Surg*. 156 (2021) 905–915. <https://doi.org/10.1001/jamasurg.2021.3301>.
- [126] M.D. Curtis, L. Villani, A. Polo, Increase of stillbirth and decrease of late preterm infants during the COVID-19 pandemic lockdown, *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 106 (2021) 456–456. <https://doi.org/10.1136/archdischild-2020-320682>.
- [127] B. Pasternak, M. Neovius, J. Söderling, M. Ahlberg, M. Norman, J.F. Ludvigsson, O. Stephansson, Preterm Birth and Stillbirth During the COVID-19 Pandemic in Sweden: A Nationwide Cohort Study, *Ann Intern Med*. 174 (2021) 873–875. <https://doi.org/10.7326/M20-6367>.
- [128] E. Toprak, A.N. Bulut, The effect of mask use on maternal oxygen saturation in term pregnancies during the COVID-19 process, *Journal of Perinatal Medicine*. 49 (2021) 148–152. <https://doi.org/10.1515/jpm-2020-0422>.

- [129] R.F. Burton, Intracellular buffering, *Respiration Physiology*. 33 (1978) 51–58. [https://doi.org/10.1016/0034-5687\(78\)90083-X](https://doi.org/10.1016/0034-5687(78)90083-X).
- [130] Eckenhoff RG, Longnecker DE., Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th ed. | Sigma-Aldrich, (Hardman JG,ed). McGraw Hill, 355-356, (n.d.). <http://www.sigmaaldrich.com/> (accessed November 7, 2021).
- [131] M.M. Adeva-Andany, N. Carneiro-Freire, C. Donapetry-García, E. Rañal-Muñño, Y. López-Pereiro, The Importance of the Ionic Product for Water to Understand the Physiology of the Acid-Base Balance in Humans, *BioMed Research International*. 2014 (2014) e695281. <https://doi.org/10.1155/2014/695281>.
- [132] I.G. Kim, B.H. Jo, D.G. Kang, C.S. Kim, Y.S. Choi, H.J. Cha, Biomineralization-based conversion of carbon dioxide to calcium carbonate using recombinant carbonic anhydrase, *Chemosphere*. 87 (2012) 1091–1096. <https://doi.org/10.1016/j.chemosphere.2012.02.003>.
- [133] M.C. Wallingford, C. Benson, N.W. Chavkin, M.T. Chin, M.G. Frasch, Placental Vascular Calcification and Cardiovascular Health: It Is Time to Determine How Much of Maternal and Offspring Health Is Written in Stone, *Frontiers in Physiology*. 9 (2018) 1044. <https://doi.org/10.3389/fphys.2018.01044>.
- [134] K.H. Chen, L.R. Chen, Y.H. Lee, Exploring the relationship between preterm placental calcification and adverse maternal and fetal outcome, *Ultrasound in Obstetrics & Gynecology*. 37 (2011) 328–334. <https://doi.org/10.1002/uog.7733>.
- [135] K.-H. Chen, K.-M. Seow, L.-R. Chen, The role of preterm placental calcification on assessing risks of stillbirth, *Placenta*. 36 (2015) 1039–1044. <https://doi.org/10.1016/j.placenta.2015.06.015>.
- [136] Benjamin Ezraty, Maïalène Chabalier, Adrien Ducret, Etienne Maisonneuve, Sam Dukan, CO<sub>2</sub> exacerbates oxygen toxicity, *EMBO Reports*. 12 (2011) 321–326. <https://doi.org/10.1038/embor.2011.7>.
- [137] S.R. Thom, V.M. Bhopale, J. Hu, M. Yang, Inflammatory responses to acute elevations of carbon dioxide in mice, *Journal of Applied Physiology*. 123 (2017) 297–302. <https://doi.org/10.1152/jappphysiol.00343.2017>.
- [138] A. Beheshti, E. Cekanaviciute, D.J. Smith, S.V. Costes, Global transcriptomic analysis suggests carbon dioxide as an environmental stressor in spaceflight: A systems biology GeneLab case study, *Sci Rep*. 8 (2018) 4191. <https://doi.org/10.1038/s41598-018-22613-1>.
- [139] D. Zappulla, Environmental Stress, Erythrocyte Dysfunctions, Inflammation, and the Metabolic Syndrome: Adaptations to CO<sub>2</sub> Increases?, *Journal of the CardioMetabolic Syndrome*. 3 (2008) 30–34. <https://doi.org/10.1111/j.1559-4572.2008.07263.x>.
- [140] S. Löb, N. Amann, C. Kuhn, E. Schmoeckel, A. Wöckel, A. Zati zehni, T. Kaltofen, S. Keckstein, J.-N. Mumm, S. Meister, T. Kolben, S. Mahner, U. Jeschke, T. Vilsmaier, Interleukin-1 beta is significantly upregulated in the decidua of spontaneous and recurrent miscarriage placentas, *Journal of Reproductive Immunology*. 144 (2021) 103283. <https://doi.org/10.1016/j.jri.2021.103283>.
- [141] S.C. Deoni, J. Beauchemin, A. Volpe, V. D'Sa, the R. Consortium, Impact of the COVID-19 Pandemic on Early Child Cognitive Development: Initial Findings in a Longitudinal Observational Study of Child Health, 2021. <https://doi.org/10.1101/2021.08.10.21261846>.

- [142] R.N. Wine, C.A. McPherson, G.J. Harry, IGF-1 and pAKT Signaling Promote Hippocampal CA1 Neuronal Survival Following Injury to Dentate Granule Cells, *Neurotox Res.* 16 (2009) 280–292. <https://doi.org/10.1007/s12640-009-9060-y>.
- [143] I. Aksu, M. Ates, B. Baykara, M. Kiray, A.R. Sisman, E. Buyuk, B. Baykara, C. Cetinkaya, H. Gumus, N. Uysal, Anxiety correlates to decreased blood and prefrontal cortex IGF-1 levels in streptozotocin induced diabetes, *Neurosci Lett.* 531 (2012) 176–181. <https://doi.org/10.1016/j.neulet.2012.10.045>.
- [144] I. Aksu, B. Baykara, M. Kiray, T. Gurpinar, A.R. Sisman, N. Ekerbicer, A. Tas, O. Gokdemir-Yazar, N. Uysal, Serum IGF-1 levels correlate negatively to liver damage in diabetic rats, *Biotechnic & Histochemistry.* 88 (2013) 194–201. <https://doi.org/10.3109/10520295.2012.758311>.
- [145] N. Uysal, K. Tugyan, B.M. Kayatekin, O. Acikgoz, H.A. Bagriyanik, S. Gonenc, D. Ozdemir, I. Aksu, A. Topcu, I. Semin, The effects of regular aerobic exercise in adolescent period on hippocampal neuron density, apoptosis and spatial memory, *Neuroscience Letters.* 383 (2005) 241–245. <https://doi.org/10.1016/j.neulet.2005.04.054>.
- [146] N. Uysal, S. Gonenc, O. Acikgoz, C. Pekçetin, B.M. Kayatekin, A. Sonmez, I. Semin, Age-dependent effects of maternal deprivation on oxidative stress in infant rat brain, *Neurosci Lett.* 384 (2005) 98–101. <https://doi.org/10.1016/j.neulet.2005.04.052>.
- [147] N. Uysal, A.R. Sisman, A. Dayi, S. Ozbal, F. Cetin, B. Baykara, I. Aksu, A. Tas, S.A. Cavus, S. Gonenc-Arda, E. Buyuk, Acute footshock-stress increases spatial learning-memory and correlates to increased hippocampal BDNF and VEGF and cell numbers in adolescent male and female rats, *Neurosci Lett.* 514 (2012) 141–146. <https://doi.org/10.1016/j.neulet.2012.02.049>.
- [148] K. Tugyan, N. Uysal, D. Ozdemir, U. Sonmez, C. Pekçetin, G. Erbil, A. Sonmez, Protective effect of melatonin against maternal deprivation-induced acute hippocampal damage in infant rats, *Neurosci Lett.* 398 (2006) 145–150. <https://doi.org/10.1016/j.neulet.2005.12.090>.
- [149] A. Sikter, G. Faludi, Z. Rihmer, The role of carbon dioxide (and intracellular pH) in the pathomechanism of several mental disorders. Are the diseases of civilization caused by learnt behaviour, not the stress itself?, *Neuropsychopharmacol Hung.* 11 (2009) 161–173.
- [150] W.E. Hoffman, F.T. Charbel, G. Edelman, J.I. Ausman, Brain tissue acid-base response to hypercapnia in neurosurgical patients, *Neurol Res.* 17 (1995) 417–420.
- [151] X. Huo, J. Min, C. Pan, C. Zhao, L. Pan, F. Gui, L. Jin, X. Wang, Efficacy of Lovastatin on Learning and Memory Deficits Caused by Chronic Intermittent Hypoxia-Hypercapnia: Through Regulation of NR2B-Containing NMDA Receptor-ERK Pathway, *PLOS ONE.* 9 (2014) e94278. <https://doi.org/10.1371/journal.pone.0094278>.
- [152] F.A. Dodge, R. Rahamimoff, Co-operative action a calcium ions in transmitter release at the neuromuscular junction, *J Physiol.* 193 (1967) 419–432. <https://doi.org/10.1113/jphysiol.1967.sp008367>.
- [153] G.C. Tombaugh, G.G. Somjen, Differential sensitivity to intracellular pH among high- and low-threshold Ca<sup>2+</sup> currents in isolated rat CA1 neurons, *J Neurophysiol.* 77 (1997) 639–653. <https://doi.org/10.1152/jn.1997.77.2.639>.
- [154] K.B. Hota, S.K. Hota, O.P. Chaurasia, S.B. Singh, Acetyl-L-carnitine-mediated neuroprotection during hypoxia is attributed to ERK1/2-Nrf2-regulated mitochondrial biosynthesis, *Hippocampus.* 22 (2012) 723–736. <https://doi.org/10.1002/hipo.20934>.



- [155] MPG - nichtamtliches Inhaltsverzeichnis, (n.d.). <https://www.gesetze-im-internet.de/mpg/> (accessed June 6, 2021).
- [156] REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, (n.d.). <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=DE> (accessed January 1, 2023).
- [157] L. Fearnley, X. Wu, Beyond Asian ‘mask culture’: understanding the ethics of face masks during the Covid-19 pandemic in Singapore, *Critical Public Health*. 0 (2022) 1–12. <https://doi.org/10.1080/09581596.2022.2114315>.
- [158] C. Stanton, J.E. Lawn, H. Rahman, K. Wilczynska-Ketende, K. Hill, Stillbirth rates: delivering estimates in 190 countries, *Lancet*. 367 (2006) 1487–1494. [https://doi.org/10.1016/S0140-6736\(06\)68586-3](https://doi.org/10.1016/S0140-6736(06)68586-3).
- [159] B. Gubhaju, Fertility Decline in Asia: Opportunities and Challenges, *The Japanese Journal of Population*. Vol.5, No.1 (2007) 19–42.
- [160] Y.A. Cheng, Ultra-low fertility in East Asia: Confucianism and its discontents, *Vienna Yearbook of Population Research*. 18 (2020) 83–120.
- [161] W.H. Organization, Mask use in the context of COVID-19: interim guidance, 1 December 2020, (2020). <https://apps.who.int/iris/handle/10665/337199> (accessed May 13, 2021).
- [162] P. Bagus, J.A. Peña-Ramos, A. Sánchez-Bayón, COVID-19 and the Political Economy of Mass Hysteria, *International Journal of Environmental Research and Public Health*. 18 (2021) 1376. <https://doi.org/10.3390/ijerph18041376>.
- [163] A.-L. Sorg, M. Hufnagel, M. Doenhardt, N. Diffloth, H. Schrotten, R. von Kries, R. Berner, J. Armann, Risk for severe outcomes of COVID-19 and PIMS-TS in children with SARS-CoV-2 infection in Germany, *Eur J Pediatr*. 181 (2022) 3635–3643. <https://doi.org/10.1007/s00431-022-04587-5>.
- [164] WMA - The World Medical Association-Declaration of Helsinki, (n.d.). <https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/> (accessed November 8, 2021).
- [165] WMA - The World Medical Association-WMA Declaration of Lisbon on the Rights of the Patient, (n.d.). <https://www.wma.net/policies-post/wma-declaration-of-lisbon-on-the-rights-of-the-patient/> (accessed November 8, 2021).
- [166] Nuremberg Code, United States Holocaust Memorial Museum. (n.d.). <https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code> (accessed November 8, 2021).
- [167] M. Bayati, D.C. Vu, P.H. Vo, E. Rogers, J. Park, T.L. Ho, A.N. Davis, Z. Gulseven, G. Carlo, F. Palermo, J.A. McElroy, S.C. Nagel, C.-H. Lin, Health risk assessment of volatile organic compounds at daycare facilities, *Indoor Air*. 31 (2021) 977–988. <https://doi.org/10.1111/ina.12801>.
- [168] S. Kerkeling, C. Sandten, T. Schupp, M. Kreyenschmidt, VOC emissions from particle filtering half masks – methods, risks and need for further action, *EXCLI Journal*. 20 (2021) 995–1008. <https://doi.org/10.17179/excli2021-3734>.

- [169] G. Töndury, *Entwicklungsgeschichte und Fehlbildungen der Wirbelsäule*, Hippokrates-Verlag, 1958.
- [170] H. Meessen, Chronic Carbon Dioxide Poisoning. *Experimental Studies.*, *Arch. Pathol.* 45 (1948) 36–40.
- [171] K.B. Karnauskas, S.L. Miller, A.C. Schapiro, Fossil Fuel Combustion Is Driving Indoor CO<sub>2</sub> Toward Levels Harmful to Human Cognition, *GeoHealth.* 4 (2020) e2019GH000237. <https://doi.org/10.1029/2019GH000237>.
- [172] C.M. Duarte, Ł. Jaremko, M. Jaremko, Hypothesis: Potentially Systemic Impacts of Elevated CO<sub>2</sub> on the Human Proteome and Health, *Frontiers in Public Health.* 8 (2020). <https://www.frontiersin.org/articles/10.3389/fpubh.2020.543322> (accessed January 1, 2023).

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