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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-CoV-2-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_2. 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_2 exposure and facemask use.

Results: Fresh air has around 0.04% CO_2, while wearing masks more than 5 min 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_2 based on animal studies which indicated an increased risk for stillbirths. Additionally, mammals who were chronically exposed to 0.3% CO_2 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_2 exposure has to be defined as being toxic. Additional data exists on the exposure of chronic 0.3% CO_2 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_2 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

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performance in children born during the pandemic. A need exists to reconsider mask mandates.

Keywords: Adolescents; Carbon dioxide (CO2) exposure; Children; Health risk assessment; Long-term adverse effects; MIES-Syndrome; N95 face mask; Pregnant women; Surgical mask; Toxicity.

Figures

Fig. 1 Flow diagram according to the...

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Jeffrey H. Anderson

The Harm Caused by Masks

A new study suggests that the excess carbon dioxide breathed in by mask-wearers can have major health consequences.

/ Eye on the News / Health Care May 09 2023

Evidence continues to mount that mask mandates were perhaps the worst public-health intervention in modern American history. While concluding that wearing masks "probably makes little or no difference" in preventing the spread of viruses, a recent Cochrane review also emphasized that "more attention should be paid to describing and quantifying the harms" that may come from wearing masks. A new study from Germany does just that, and it suggests that the excess carbon dioxide breathed in by mask-wearers may have substantial ill-effects on their health—and, in the case of pregnant women, their unborn children's.

Mask-wearers breathe in greater amounts of air that should have been expelled from their bodies and released out into the open. "[A] significant rise in carbon dioxide occurring while wearing a mask is scientifically proven in many studies," write the German authors. "Fresh air has around 0.04% CO2," they observe, while chronic exposure at CO2 levels of 0.3 percent is "toxic." How much CO2 do mask-wearers breathe in? The authors write that "masks bear a possible chronic exposure to low level carbon dioxide of 1.41–3.2% CO2 of the inhaled air in reliable human experiments."

In other words, while eight times the normal level of carbon dioxide is toxic, research suggests that mask-wearers (specifically those who wear masks for more than 5 minutes at a time) are breathing in 35 to 80 times normal levels.

The German study, a scoping review of existing research, aimed "to investigate the toxicological effects of face masks in terms of CO2 rebreathing on developing life,

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specifically for pregnant women, children, and adolescents." The latter two groups, of course, have been among those most frequently subjected to mask mandates in schools, despite Covid's low levels of risk for them and the evidence that masks don't work.

What can breathing too much carbon dioxide do to you? The authors write that "at levels between 0.05% and 0.5% CO2," one might experience an "increased heart rate, increased blood pressure and overall increased circulation with the symptoms of headache, fatigue, difficulty concentrating, dizziness, rhinitis, and dry cough." Rates above 0.5 percent can lead to "reduced cognitive performance, impaired decision-making and reduced speed of cognitive solutions." Beyond 1 percent, "the harmful effects include respiratory acidosis, metabolic stress, increased blood flow and decreased exercise tolerance." Again, mask-wearers are likely breathing in CO2 levels between 1.4 percent and 3.2 percent—well above any of these thresholds. What's more, "Testes metabolism and cell respiration have been shown to be inhibited increasingly by rising levels of CO2."

So, high blood pressure, reduced thinking ability, respiratory problems, and reproductive concerns are among the many possible results of effectively poisoning oneself by breathing in too much carbon dioxide.

The authors write that "it is clear that carbon dioxide rebreathing, especially when using N95 masks, is above the 0.8% CO2 limit set by the US Navy to reduce the risk of stillbirths and birth defects on submarines with female personnel who may be pregnant." In other words, mandates have forced pregnant women to wear masks resulting in levels of CO2 inhalation that would be prohibited if they were serving on a Navy submarine.

Indeed, according to the authors, there exists "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." They cite recent data from Australia, which "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 stillborn births." Meantime, "no

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increased risk of stillbirths was observed in Sweden," which famously defied the public-health cabal and went its own way in setting Covid policies.

As for countries where mask-wearing has long been common, the authors write, "Even before the pandemic, in Asia the stillbirth rates have been significantly higher" than in Eurasia, Oceania, or North Africa.

"It has to be pointed out that this data on the toxicity of carbon dioxide on reproduction has been known for 60 years," the authors observe. For this reason, they write, the National Institute for Occupational Safety and Health (NIOSH), which is part of the Centers for Disease Control and Prevention (CDC), has CO2 threshold limits of 3 percent for 15 minutes and 0.5 percent for eight hours in workplace ambient air. Yet the CDC has been perhaps the primary pusher of masks in the United States.

Nor is increased CO2 intake the only health danger that results from wearing masks. The study focused only on CO2, but the authors note that "other noxious agents in the masks contribute to toxicological long-term effects like the inhalation of synthetic microfibers, carcinogenic compounds and volatile organic compounds." They add that "the increased carbon dioxide content of the breathing air behind the mask may also lead to a displacement of oxygen." Masks are also uncomfortable and unhygienic, and they profoundly compromise human social interaction.

In light of all this, it seems indefensible to mandate—or even to advise—the wearing of masks, especially among the young. The authors write, "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."

Public-health officials—and the executive-branch leaders who credulously listened to them—ignored centuries of Western norms, the best medical evidence, and common sense, deciding that their own novel and evidence-free course was the one that all of society should be forced to follow. We should never again indulge such an obvious and destructive misstep.

Jeffrey H. Anderson is president of the American Main Street Initiative, a think tank for everyday Americans. He served as director of the Bureau of Justice Statistics at the U.S. Department of Justice from 2017 to 2021.

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Kai Kisielinski, Susanne Wagner, [...], and Andreas Prescher

Abstract

Introduction

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As part of a scoping review, literature was systematically reviewed regarding CO_2 exposure and facemask use.

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Fresh air has around 0.04% CO_2, while wearing masks more than 5 min 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_2 based on animal studies which indicated an increased risk for stillbirths. Additionally, mammals who were chronically exposed to 0.3% CO_2 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_2 exposure has to be defined as being toxic. Additional data exists on the exposure of chronic 0.3% CO_2 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_2 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.

Keywords: Carbon dioxide (CO_2) exposure, Toxicity, N95 face mask, Surgical mask, Long-term adverse effects, Health risk assessment, MIES-Syndrome, Children, Adolescents, Pregnant women

1. Introduction

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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], [3], [4], [5], [6]]. In this paper, we highlight the toxicological aspects of wearing a mask for special user groups resulting from a low-level CO_2 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 μm 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 μm, 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], [12], [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 study only points 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. Moreover, 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 reduce relevance of statements derived from them: Due to standard deviations, they lie between 40% and 100% (Wuhan, Singapore, Gainesville and Omaha), and 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 Pinf-values (1%–100%) is noted [12]. The modelling of the aerosol particle penetration (<100 μm) 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 μm diameter range from 20 up to 80%, exhibiting a large deviation [12]. Naked viroids of less than 1 μm in diameter (e.g. 0.06–0.12 μm 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 μm 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 μm 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

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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, requires further investigation.

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-CoV-2 [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], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [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 evidence for the efficacy of masks against viral transmission within the general population, from a purely evidence-based empirical perspective, masks for the public may be overrated in a pandemic response [[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 Catalonian 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 discomfort. 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-min 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 studies, the

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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_2-inhalation: Physiological changes already occur at levels between 0.05% and 0.5% CO_2 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_2 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_2 the harmful effects include respiratory acidosis, metabolic stress, increased blood flow and decreased exercise tolerance [55]. Therefore, regarding low-level CO_2 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 min for 3% for short periods, while the 8-h limit is set at 0.5% CO2 [57].

With female submarine crews entering the U.S. Army in November 2011, a reassessment of CO_2 limits was conducted back in 2012, focusing on potential reproductive and developmental effects. Inspired by this US Navy report on potentially harmful CO_2 values for female submarine crews based on animal studies [58] and the fact that increased CO_2 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_2 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 November 30, 2021 on toxic effects of low-level carbon dioxide (≤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_2 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_2 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_2), 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_2 when using a mask. Four reviews describe the toxicity of inhaled low level CO_2. 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. Fig. 1 shows the flow chart of our scoping review.

Fig. 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 thesis research study) focusing on possible rebreathing 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 min [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_2 vol%) was measured in the air under the masks after few minutes. The concentrations of 14 162 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_2 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 min is at least 0.9% CO_2 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_2 per breath during simulations of eight breathing cycles in 33.65 s (see video in mentioned publication with animation of CO_2 distribution with and without a respirator)[67]. Another modeling study shows that wearing N95 masks results in carbon dioxide accumulation, the volume fraction of CO_2 reaches 1.2% after 7 breathing cycles and is then maintained at 3.04% on average. The wearers re-inhale excessive CO_2 with every breath taken from the mask cavity [68].

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In 2013 Sinkule already evaluated 30 different N95 respirators using the NIOSH Automated Breathing and Metabolic Simulator (ABMS) through 5 min work rates and found elevated CO_2 levels in the inhaled air ranging between 1.28% and 3.52% [69]. These results are consistent with measurements of CO_2 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 min 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 min. Serial CO_2 measurements were performed with a nasal cannula at a frequency of 1 Hz [73]. The measured 2.4–2.6% CO_2 concentration translates into a highly significant increase in CO_2 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_2 – in workplace ambient air [57]. Rhee's quality study (serial CO_2 measurements with a high performance CO_2 sensor at a frequency of 1 Hz for 15 min) demonstrates a significant increase in end-tidal CO_2 concentrations among healthy volunteers while donning KN95 respirators. Consequently, the authors recommended further studies.

Table 1 summarizes the experimental findings concerning CO_2-re-breathing under face masks.

Table 1

Experimentally measured CO_2 concentrations in the inhaled air under masks.

When masks are used elevated CO_2 concentrations are inhaled [[64], [65], [66], [67], [68], [69], [70], [71], [72], [73]]. It also has the potential to exceed acute (3% CO_2 for 15 min) and chronic (0.5% CO_2 for 8 h) NIOSH limits for CO_2 respiration (Table 1). Despite the compensatory mechanisms that occur (e.g. lowered blood pH, increased respiratory rate and ventilation) [74,75] an arterial $PaCO_2$ rise is inevitable in the long term [76]. For example, breathing air with an inspired CO_2 fraction of 1% (≈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_2 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_2 content during mask use [64,[76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [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 participantś 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_2 outcomes [93]. However, some studies with continuous measurement of physiological parameters including $PtCO_2$ in all subjects also found no statistical difference between mask and no mask use, though measured CO_2 levels were continuously higher in mask wearers [71,95]. Some of these studies were conducted under extreme conditions (1 h 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_2 was observed while wearing N95 masks. In the literature found, this phenomenon is attributed to the fact that

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the dead space volume is almost doubled and the breathing resistance is more than doubled, which leads to a significant re-breathing of CO_2 with every breathing cycle [48,67,68]. Due to compensatory mechanisms, carbon dioxide partial pressure ($PaCO_2$) 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_2 [79].

Table 2

Significant increase in CO_2 levels in mask wearers under various conditions in scientific intervention studies.

In summary, the build-up of CO_2 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_2 for 8 h) and even acute (3% CO_2 for 15 min) [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.

3.2. General effects of CO_2 breathing in low concentrations (≤ 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_2 levels above 1% an increase in cardiac output is seen. Inhalation of between 2.5 and 3.5% carbon dioxide for up to 10 min 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_2 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], [68], [69], [70], [71],73]. In the human experiments with low level 1–2% CO_2 exposure an increased respiratory minute volume of more than 34% was detected [75]. Moreover, higher arterial $PaCO_2$ and bicarbonate levels produced an effective buffering of inhaled CO_2. A correlation could be shown between changes in plasma calcium level, pH, and CO_2, indicating that the bone CO_2 store is a determining factor in the extended time periods of CO_2 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], [102], [103], [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].

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3.3. Circumstantial evidence for specific mask effects: low-level inhaled CO_2 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 (≤ 3%) are presented. They provide information on possible mask effects. It should be mentioned that in a toxicology study [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_2 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_2 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 h [58,107].

3.3.2. Low level CO_2 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 0.1–0.3%, 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_2 the pups demonstrated increased anxiety [108], which is even more pronounced when the pregnant mother animals were exposed to 0.3% CO_2.

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 h 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 s 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 s 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 CO_2-induced loss of neurons is irreversible.

3.3.3. Low level CO_2 inhalation: male reproductive toxicity As a rise in carbon dioxide when wearing a mask is scientifically proven (Table 1, Table 2), 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

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studied extensively in animal experiments. The exposure of adolescent rats to a carbon dioxide level of 2.5% once for 4 h 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 h a day [58,107,114,115].

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

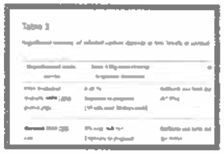

Table 3

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

4. Discussion

The above data including Table 1, Table 2, 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_2 concentrations in the inhaled air under masks can reach – depending on exposure time – values of 0.42 up to 3.52 vol% (Table 1). One has to remember, that in those experiments the time measured wearing a mask ranged from 1 min to several minutes with a maximum of 60 min 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_2 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_2 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_2 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_2 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_2 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_2) and 15 min (3% CO_2) 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_2 in the majority of studies with values above 1% [64,65,[67], [68], [69], [70], [71],73] including Table 1, it is clear that carbon dioxide rebreathing, especially when using N95 masks, is above the 0.8% CO_2 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 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-CoV-2 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

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(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_2 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_2 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_2 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_2 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_2 stress a metabolic acidosis occurs and the kidneys no longer respond in producing bicarbonate [101]. Thereafter –with a further prolonged CO_2 burden – the body uses the bones to regulate the acid levels in the blood: Bicarbonate and a positive ion (Ca^{2+}, K^+, Na^+) are exchanged for H^+. 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_2 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_2 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_2 or an 8-week exposure to 0.5% CO_2 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], [134], [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_2 exposure in humans and animals [56,112,[137], [138], [139]]. CO_2 increases the result in higher levels of pro-inflammatory Interleukin-1β, a protein involved in regulating immune responses, which causes inflammation and vascular damage [137]. Significant upregulation of IL-1β 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-1β at the fetomaternal interface and its crucial role in miscarriage processes has been studied including such elevated protein expression of IL-1β 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 (Table 1 and 2) [[64], [65], [66], [67], [68], [69], [70], [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_2 under masks can rise to levels far higher than 1% as mentioned above [64,65,[67], [68], [69], [70], [71],73], especially when masks are worn in closed buildings additionally worsening the sick building syndrome [55,56]. A look at Table 1, Table 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_2 exposition of higher than 0.3% while using a face mask. After low-level exposure of 0.3% CO_2 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 (Table 1, Table 2, Table 3). Regarding the experimentally measured CO_2 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], [65], [66], [67], [68], [69], [70], [71], [72], [73]], the results from Table 3 [113,114] are remarkable. In 2014 Uysal could demonstrate with his experiments that a mere 0.3% CO_2 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_2 is prolonged (several hours to one week) the organism depletes its buffer systems [113,[142], [143], [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_2-exposure the latter occurs, especially under exercise or stress [[145], [146], [147], [148]]. Blood carbon dioxide concentration exerts an important influence on intra- and extracellular pH. CO_2 passes quickly through the cell membranes to form carbonic acid with H_2O, which releases H^+ ions and, in excess, causes acidosis [[149], [150], [151]]. Acidosis decreases transmembrane Ca^{2+} 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-h low level CO_2 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_2 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], [65], [66], [67], [68], [69], [70], [71],73] especially when room air (in crowded classrooms) already has an increased CO_2 content [55,56,112]. The damaging mechanism of CO_2 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], [137], [138], [139]]. Testes metabolism and cell respiration have been shown to be inhibited increasingly by rising levels of CO_2 [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_2 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-h exposure limit of 0.5% CO_2 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 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, 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

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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-CoV-2 [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-CoV-2 in widespread use, especially regarding our referenced data with possible deleterious effects for children, adolescents and pregnant women. The background of the decisions on far-reaching mandatory mask use must be supported by additional scientific studies [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-CoV-2 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], [125], [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_2 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_2, 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 teratogenetic 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].

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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_2 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_2 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, especially for N95-masks (Table 2) due to their higher deadspace and breathing resistance [48].

Fresh air has around 0.04% CO_2 while masks bear a possible chronic exposure to low level carbon dioxide of 1.41–3.2% CO_2 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_2 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], [107], [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], [125], [126],141].

According to the data found, wearing face masks also has the potential to exceed acute (3% CO_2 for 15 min) and chronic (0.5% CO_2 for 8 h) NIOSH limits for CO_2 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], [118], [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_2 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_2 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.

Ethics approval and consent to participate

Not applicable.

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Consent for publication

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