Physio-metabolic and clinical consequences of wearing face masks -Systematic review with meta-analysis and comprehensive evaluation

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Systematic Review

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Physio-metabolic and clinical consequences of wearing face masks -Systematic review with meta-analysis and comprehensive evaluation

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Abstract

Background: As face masks are a mandatory public health intervention during the COVID-19 pandemic, adverse effects require substantiated investigation.
Methods: A systematic review of 2168 studies yielded 54 publications for synthesis and 37 studies for meta-analysis (on n=8641, m=2482, f=6159, age=34.8±12.5). The median trial duration was only 18 min (IQR=50) for our comprehensive evaluation of mask induced physio-metabolic and clinical outcomes.
Results: We found significant effects in both medical masks with a greater impact regarding the N95. These effects included decreased SpO_2 (overall SMD=-0.24, 95%CI=-0.38 to -0.11, p=0.0004) and minute ventilation (SMD=-0.72, 95%CI=-0.99 to -0.46, p<0.00001), simultaneously increased blood-CO_2 (SMD=+0.64, 95%CI=0.31–0.96, p=0.0001), heart rate (N95: SMD=+0.22, 95%CI=0.03–0.41, p=0.02), systolic blood pressure (surgical: SMD=+0.21, 95%CI=0.03–0.39, p=0.02), skin temperature (overall SMD=+0.80 95%CI 0.23–1.38, p=0.006) and humidity (SMD +2.24, 95%CI=1.32–3.17, p<0.00001). Effects on exertion (overall SMD=+0.9, surgical=+0.63, N95=+1.19), discomfort (SMD=+1.16), dyspnoea (SMD=+1.46), heat (SMD=+0.70) and humidity (SMD=+0.9) were significant in 373 cases with a robust relationship to mask wearing (p<0.006 to p<0.00001). Pooled symptom prevalence was significant in users (n=8128) for: headache (62%, p<0.00001), acne (38%, p<0.00001), skin irritation (36%, p<0.00001), dyspnoea (33%, p<0.00001), heat (26%, p<0.00001), itching (26%, p<0.00001), voice disorder (23%, p<0.03) and dizziness (5%, p=0.01).
Discussion: Masks interfered with O_2-uptake and CO_2-release and compromised respiratory compensation. Though evaluated wearing durations do not represent daily/prolonged use, outcomes independently validate mask-induced exhaustion-syndrome (MIES). MIES can have long-term clinical consequences, especially for vulnerable groups.
Conclusion: Face mask side-effects must be assessed (risk-benefit) against the available evidence of their effectiveness against viral transmissions.

Introduction

The use of face masks has been restricted to professionals for decades. In the health-care setting, masks constituted a mandatory self-protective and third-party protective measure for medical personnel prior to COVID-19 pandemic and there is no doubt about the efficacy of masks in reducing transmission of pathogens, especially bacteria. In 2020, many scientists and leaders started to believe that the use of masks could also provide protection against viral transmission, although evidence for the effectiveness of this measure was only weak [1]. In the meantime, a large number of publications on this topic cannot be overlooked [2,3].

During the 2019 SARS-CoV-2 outbreak face masks were deployed as a mandatory public health measure for the general population in many countries around the world, making them one of the most important universal life-style attributes that directly affects how we breathe. As with any other preventive measure and/or intervention, masks also have specific advantages and disadvantages. While certain properties may have justified their invention and application in the past, e.g. retention of bacteria during surgical wound care and operations, at present the question needs to be addressed as to the long-term effects widespread mask wearing may have on normal breathing. It is noteworthy that the compulsory wearing of masks for the entire population provided good research conditions and consequently numerous publications dealing with the adverse effects of mask wearing [4–11]. Various volatile metabolites are produced from *in vivo* biochemical and metabolic pathways and their concentrations in exhaled breath provide immediate physiological [12,13], metabolic [14,15] and pathological [16,17] magnitudes with the possibility of monitoring various processes and interventions including therapies [18,19]. A recent observational study reported continuous respiratory and haemodynamic changes along with corresponding alteration in exhaled volatile metabolites (viz. potentially originate at the cellular/organ levels and via microbial metabolic processes) and has raised significant concerns upon the immediate, progressive, transient and long-term side-effects of FFP2/N95 and surgical masks in adults (aged between 20 – 80 years) at rest [20]. Previously, based on other numerous publications major concerns were raised in a large-scale scoping review [8]. Furthermore, this recent scoping review on mask driven adverse effects and health risks has summoned for a systematic review.

Though some important systematic reviews regarding masks and their effects already exist [21–24], they are predominantly restricted to healthy and sportive individuals [21,23]. Due to the exclusion of children, pregnant women and diseased patients from these evaluations and conclusions [22,25], the reviews do not provide sufficient evidence that masks can be employed in the general population as safe protective measures. Moreover, the application of fixed statistical models [21], use of narratives rather than quantitative analysis and statistics (despite claiming to be systematic) [26], focus only on health care workers and their complaints [25], as well as comparing the different mask types without any baseline/control group [25] were ubiquitous limitations of those studies. Physiological systematic reviews based purely on physiological effects of masks limit data interpretations to normal physio-metabolic fluctuations i.e. beyond the domain of pathophysiological compensatory mechanisms (especially in the elderly and those with diminished compensatory reserves) and/or acute/chronic subliminal changes in the human microbiome [22,24]. Similarly, other manuscripts do not address subjective parameters, prevalence of symptoms and discomfort during mask use and concomitant physical changes such as heat and temperature in detail [21,23]. Therefore, the systematic reviews available to date neither address possible symptoms of mask use for the general population nor their exact prevalence. In addition, the transferability of the outcomes of said systematic reviews to the general population is very limited and they do not fulfil the actual requirements of clinical and inclusive evaluation, especially from the views and perspective of physicians and clinicians. Including young, old, healthy and ill people for the systematic analysis of physiological, metabolic and clinical data could complete the possible comprehensive impact of mask-wearing on the general population. In contrast to the above-indicated studies, our systematic review is aimed to quantify the biochemical/metabolic, physical, physiological changes along with the appearance of subjective and clinical symptoms in face mask users and analyse them form a clinician´s and physician´s holistic perspective.

Materials & Methods

Registration

This meta-analysis was registered with the international prospective register of systematic reviews (PROSPERO) under the record CRD42021256694 at the National Institute for Health Research (NIHR) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [27].

Inclusion and exclusion criteria

The aim was to study adverse effects of face masks on metabolic, physiological, physical, psychological and individualised parameters. The use of cloth masks, surgical masks and N95/FFP-2 masks were the intervention of interest. Humans of all ages and genders, who were evaluated in controlled intervention studies and observational studies have been included in our comprehensive evaluation. Case reports, narrative reviews, case series and expert opinions were excluded. The main outcomes considered were peripheral oxygen saturation (SpO_2), carbon dioxide levels in blood, temperature, humidity, heart rate, respiratory rate, tidal volume and minute ventilation, blood pressure, exertion, dyspnoea, discomfort, headache, skin changes, itching, psychological stress and symptoms during the use of face masks.

Literature retrieval strategy

First, a comprehensive search term was developed. Then, PubMed, Embase and Cochrane Library databases were searched. The search was performed until 31st December 2021. There were no restrictions in publication date. Literature that was neither English nor German language was excluded. Additionally, forward-looking data (e.g. available as preprint, but not published in a peer-reviewed scientific journal at time of completing this meta-analysis) was considered for discussion, but not included in the meta-analysis.

Literature screening and data extraction

Search terms were created according to the criteria defined in the PICO scheme [28]. The specific search terms were: (face mask* [tw], FFP1 [tw] FFP2 [tw], FFP3 [tw], N99 [tw], N97 [tw], N95 [tw], respiratory protective device* [tw], air-purifying respirator* [tw], surgical mask* [tw]) and (risk* or adverse effect* [tw], adverse event* [tw], side effect* [tw], psycho* [tw], hypoxia [tw], hypercapnia [tw], headache [tw], dead space [tw], safety [tw], carbon dioxide [tw]), not infants, not neonatal, not newborn, not endoscopy, not CPAP, not intubate*, not propofol, not resuscitation, not mechanical ventilation [tw], not foetus. The asterisk in the search algorithm here '*' stands for the extension of the spelling with different possible letter combinations (e.g. face mask* with *= s, or *=ed, or *=ing). The abbreviation '[tw]' stands for title word.
The retrieved titles and abstracts were then screened and assessed for predefined inclusion criteria by at least three authors. Study design, methodology, interventions, primary and secondary

outcomes and language were evaluated using the web-based program Rayyan — a web and mobile app for systematic reviews [29]. Full texts of all potentially relevant articles were independently assessed for inclusion by two authors. Full-text exclusions and reasons have been documented. Data of included full texts were extracted: Author and year, type of study, aim of the study, intervention/control, sample size, follow-up, outcomes, funding, setting/country, age, sex, comorbidities, medications, functional status and cognitive status of participants, results, main findings, and limitations. Descriptive data was extracted by one author and checked by a senior author. If discrepancies occurred or authors disagreed, a senior author was involved in and a consensus was found [30].

Risk of bias assessment of the included studies

The quality assessments were carried out using various tools, depending on the type of study. If systematic reviews and meta-analyses were included, these were assessed using the AMSTAR-2 checklist [31]. Interventional studies were examined using the manual "Assessment of the risk of bias in clinical studies" from the Cochrane Collaboration (Cochrane RoB-2) [32]. Observational studies were checked with the CASP (Critical Appraisal Skills Program) using standardised forms [33].

Statistical analysis

A meta-analysis was carried out, if enough studies with the same research question were found among the randomised, non-randomised controlled trials and observational studies. A subgroup analysis was conducted, where possible, for different mask types (N95/surgical) and even compared the mask types with each other (N95 vs surgical mask). The program "RevMan-5.4.1", which was developed for Cochrane Reviews was used. As we anticipated a considerable between-study heterogeneity -the random effects model was used to pool effect sizes [34]. The results were graphically depicted in forest plots. Subgroup analyses were performed and a Q test was calculated to examine significant subgroup differences. Study heterogeneity was assessed using Cochrane´s Q test, T2 according to DerSimonian / Laird [35], and I^2 according to Higgins / Thompson [36]. Where possible, a funnel plot was created to investigate publication bias. If this showed an abnormal result and there were at least ten studies evaluating the same question, Egger´s test [37] was carried out.
For the analysis of metabolic and physiological changes all controlled intervention studies in which measurements were taken during physical activity with face masks were included. We excluded resting conditions since these are not representative for real life settings and pre-post studies to ensure study-comparability. In addition, by excluding rest situations of the mostly healthy study participants, our approach was able to represent the possible effects better in elderly and ill individuals (e.g. with compromised compensation mechanisms), all of whom are a significant part of the general population. This also helped to reduce heterogeneity (I^2). Neither for the results of the systolic blood pressure (SBP) nor the temperature did we follow this approach. Studies in which measurements were taken during rest and moderate physical activity were included in the meta-analysis of the physical outcome on SBP to obtain an evaluable number of studies and to ensure a better comparability and lower heterogeneity (exclusion of heavy load exercise conditions). In order to gather more available data for evaluating the temperature, we included two pre-post studies containing a resting condition using valid methodology and exact temperature measurements. This clearly reduced the heterogeneity index I^2.For the meta-analysis of the resultant CO_2-blood-content the joint evaluation of different experimental CO_2 measurements ($PtCO_2$, $ETCO_2$, $PaCO_2$) in mmHg was justified by the following facts:
1) "$ETCO_2$ and $PtCO_2$ measurements both provide an estimation of $PaCO_2$" [38].
2) "End-tidal CO_2 ($ETCO_2$) has been considered as a reliable estimate of arterial PCO_2, in healthy subjects" [39].

3) "$PtCO_2$ reliably reflects $PaCO_2$, irrespective of sensor location" [40].
4) "Transcutaneous CO_2 ($PtCO_2$) devices provide another option for the continuous non-invasive estimation of $PaCO_2$, overcoming the limitations posed by end-tidal CO_2 analysis" [39].
5) "$ETCO_2$ monitoring tends to underestimate $PaCO_2$ levels" [38].

For meta-analysis of measured sensations, all studies in which measurements were mainly taken during physical activity were included. This helped to ensure comparability, lower heterogeneity and the above mentioned aims to draw conclusions on the general population under conditions resembling real life settings. However, an exemption was made for the sensation 'discomfort': To allow evaluable study numbers, we included one pre-post study with resting condition, however, with valid methodology and exact discomfort evaluations [41]. Even if this study had not been included, the result would be significant and unambiguous, however with a slightly larger 95% CI. Our systematic review also referenced studies aiming to assess the prevalence of sensations and symptoms under mask use. Therefore, we conducted an additional meta-analysis of these observational studies to document the pooled prevalence in mask use. Prevalence was calculated as total number of symptoms per 100 mask wearers. In studies where the standard error (SE) was not reported, we calculated it from the prevalence using the following formula: $SE = \sqrt{p (1-p) / n}$ with a 95% $CI = p \pm 1.96 \times SE$; where, p = Prevalence. This statistical approach to quantify a pooled prevalence from observational studies has been previously reported [34]. Meta-analysis was performed using RevMan (Version 5.4.1). The heterogeneity of each meta-analysis was assessed and then the random effects model was used to calculate the pooled prevalence. We conducted subgroup analysis where possible for mask type (N95/surgical). Funnel plots were used to study the possibility of publication bias as described above.
The inclusion of observational studies, particularly for the prevalence analysis in our meta-analysis is justified because these are particularly suitable to investigate exposures that are difficult or impossible to investigate in randomised controlled trials (RCTs), e.g. air pollution or smoking. In addition, observational studies are important to investigate causes with a long latency period, such as carcinogenic effects of environmental exposures or drugs [42]. Thus, possible adverse long-term effects of masks, i.e. comparable to the environmental hazards, appeared to be particularly detectable through observational studies.
Finally, the random statistical control calculations of our results were performed for quality assurance via the R software (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.1) and packages metafor, dmetar, meta [30]. Knapp-Hartung adjustments to control for the uncertainty in the estimate of the between-study heterogeneity were used in these calculations which are controversial as they result in wider confidence intervals and are also suspected to be anti-conservative even though the effects are very homogeneous [30].

Results

General findings

Literature characteristics

Of the 2168 screened records, 54 studies were included for qualitative analysis (see extraction tables, Table 1) and 37 for statistical meta-analysis (Figure 1). Among the 54 studies, 23 were intervention studies, and 31 were observational studies. The 23 intervention studies consisted of 14 randomised controlled trials (RCT´s) and 9 non-randomised controlled trials (nRCT´s). Of the 31 observational studies, 17 works raised measured values, and 14 were questionnaire studies.

Table 1 A-C: Overview of 54 included studies. A randomised controlled trials, B non-randomised controlled trials and C observational studies

Table 1A: Included 14 randomised controlled trials

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
Bertoli 2020	Randomized, two-period cross-over self-control trial	Wearing N95 respirator vs no facemask during indirect calorimetry	N=10	5 min	oxygen consumption (VO_2), carbon dioxide production (VCO_2),Resting Energy Expenditure (REE)
Butz 2004	Blinded, randomized cross over study	Wearing two types of surgical masks vs no mask	N=15	30 min	CO_2 under masks, $PtCO_2$(partial transcutaneous CO_2 pressure) while wearing masks for 30 min, HR, RR (respiratory rate),SpO_2
Dirol 2021	Prospective randomized cross-over study	Six-minute walking test (6MWT) with and without surgical mask. Mask-discomfort questionnaire was applied before and after 6 MWT with the mask	N=100	6 min	RR, HR, SpO_2, $EtCO_2$, discomfort questionnaire
Fikenzer 2020	Prospective cross-over study	Wearing no mask (nm) vs surgical mask (sm) vs FFP2/N95 mask (ffpm), cardiopulmonary and metabolic responses monitored by ergo-spirometry and impedance cardiography	N=12	10 min	FVC (forced vital capacity), FEV1 (forced expiratory volume in 1 s), Tiffenau index, peak expiratory flow (PEF), HR, stroke volume, cardiac output, arterio-venous oxygen content difference, systolic blood pressure (SBP), diastolic blood pressure (DBP), ventilation in liters/minute (VE), RR, tidal volume (VT), pH, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), lactate Pmax, Pmax/kg, VO_2max/kg, heart rate recovery (HRR): HRR-1 min, HRR-5 min. Discomforts (VAS): humid, hot, breath resistance, itchy, tight, salty, unfit, odor,fatigue, overall discomfort.
Georgi 2020	Prospective randomized cross-over study	wearing no mask (nm) vs community vs surgical mask (sm)vs FFP2/N95 mask (ffp treadmill: baseline, 50 W, 75W,100W)	N=24	9 min	HR, RR, SBP,DBP, $PtCO_2$,SpO_2, main symptoms questionnaire
Goh 2019	Randomized, two-period cross-over	Wearing N95 respirator vs wearing N95 respirator with microfan	N=106	15 min	$EtCO_2$, comfort level with

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
	self-control trial	vs wearing no facemask during common physical activities			visual analogue scale (VAS)
Hua 2020	Prospective randomized crossover trial	Two and 4 hours after donning the masks, adverse reactions and perceived discomfort and noncompliance were measured.	N=20	240 min	Skin parameters: Skin hydration, transepidermal water loss, erythema, pH and sebum secretion
Kim J.H. 2013	Randomized, self-control trial	Wearing N95 respirator (partly with exhalation valve) vs wearing no facemask (NM) during a low-moderate work-rate (5.6km/h)	N=20	60 min	HR, RR, transcutaneous carbon dioxide, SpO2
Kim J.H. 2015	Randomized, two-period controlled trial	Wearing N95 respirator and no mask during one hour of mixed sedentary activity and moderate exercise during pregnancy vs non pregnant women	N= 16 vs 16	60 min	SBP, DBP, mean arterial pressure, HR, stroke volume, cardiac output, total peripheral resistance, RPE, SpO_2, $PtCO_2$
Kim J.H. 2016	Randomized, self-control trial	Wearing N95 respirator vs wearing P100 respirator vs wearing no mask during 1 hour of treadmill exercise (5.6 km/h) in an environmental chamber (35°C, relative humidity 50%)	N=12	60 min	Fit factor, rectal temperature, mean skin temperature, facial skin temperature under respirator, SpO2, PtCO2, HR, RR, breathing comfort, thermal sensation,exertion (Borg scale)
Mapelli 2021	interventional, prospective, randomized, double-blind and cross-over study	Wearing no mask surgical mask or N95 mask and performing consecutive cardiopulmonary exercise tests (CPETs) at least 24 hours apart but within 2 weeks	N=12	10 min	Ventilation (VE), Oxygen intake VO2, VCO2 production, respiratory gases,: exspiratory O2 (ETO2) and exspiratory CO2 (ETCO2), Heart rate (HR), hemoglobin saturation (SaO2), blood pressure (DBP and SBD), dyspnea (Borg scale), Spirometry, Maximal Inspiratory pressure (MIP) and Maximal Expiratory Pressure (MEP)
Roberge 2014	Randomized, two-period controlled trial	Wearing an N95 FFR during exercise and postural sedentary activities over a 1-hour period on pregnant women vs control	N= 22/22	60 min	Core temperature, cheek temperature, abdominal temperature, HR, RR, RPE, perceived heat (RHP)
Wong A.Y.-Y 2020	Randomized, two-period self-controlled trial	Wearing a facemask vs not wearing a facemask during graded treadmill (10% slope) walking at 4 km/h for 6 min	N=23	6 min	HR, RPE
Zhang 2021	Prospective randomized cross-over study	Exercises (cycle ergometer) with and without surgical masks (mask-on and mask-off) were analyzed	N=71	8 min	test duration, maximum power, RPE score, Borg dyspnea scale, Oxygen consumption ($V. O_2$), carbon dioxide production ($V.CO_2$), metabolic equivalent (MET), respiratory exchange

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
					rate (RER), and percentage of oxygen uptake at anaerobic threshold (AT) in predicted maximal oxygen uptake, inspiratory time (Ti), expiratory time (Te), RR, VT, VE, end-tidal oxygen partial pressure (EtO_2), $EtCO_2$, oxygen ventilation equivalent (VE/V.O2), and carbondioxide equivalent (V_E/VCO_2)

Legend:
AT, anaerobic threshold; DBP = diastolic blood pressure; $EtCO_2$ = end-tidal CO_2 partial pressure; ESRD = end stage renal disease; TEWL= trans-epidermal water loss; FEV1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; HCW = health care worker; HD=haemodialyis; HR = heart rate; MEP = maximal expiratory pressure, MET = metabolic equivalent; MIP =maximal inspiratory pressure; PEF = peak expiratory flow; PetCO2 = end-tidal carbon dioxide pressure; PetO2 =end-tidal oxygen pressure ; PI = perfusion index; PPE = personal protective equipment; $PtCo_2$ = partial transcutaneous CO_2 pressure; RER = respiratory exchange ratio; RPE = rated perceived exertion; RR = respiratory rate; RR =respiratory rate; SaO_2 =hemoglobin oxygen saturation; SBP = systolic blood pressure; SpO_2 = oxygen saturation; Te= expiratory time; Ti = inspiratory time; Ttot =Inspiratory + expiratory time; TV = tidal volume; V˙CO2 =carbon dioxide production; V˙O2 = oxygen uptake; VE = ventilation in liters/min; VE = ventilation; VT = tidal volume,

Table 1B: Included 9 non-randomised controlled trials

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
Bharatendu 2020	Cross-sectional self-control trial	Wearing N95 respirator vs no facemask	N=154	5 min	Mean flow velocity (MFV), Pulsatility index, end-tidal carbon dioxide partial pressure ($EtCO_2$)
Coniam 2005	Two-period controlled trial	Wearing surgical masks (WM) vs no facemask (NM) during oral examination	N=186	10 min	Pronunciation, vocabulary, grammar, comprehensibility, audibility
Epstein 2020	Multiple cross-over, self-control trial	Wearing N95 respirator vs wearing surgical mask vs no facemask during maximal exercise test	N16	18 min	HR, RR, SpO_2, rated perceived exertion (RPE), end-tidal carbon dioxide ($EtCO_2$)
Lee 2011	Two-period self-controlled trial	Wearing N95 respirator vs no facemask during rhinomanometry	N=14	30 sec	Inspiration breathing resistance increment, expiration breathing resistance increment, breathing volume decrement
Roberge 2010	Multiple cross-over, self-control trial	Wearing an N95 FFR vs N95 FFR with exhalation valve vs no mask during 1-hour treadmill walking sessions, at 1.7 miles/h and at 2.5 miles/h	N=10	60 min	FFR dead space gases, CO_2 saturation, O_2 saturation, RR, VT, VE, HR
Roberge 2012	Two-period self-control trial	Wearing a surgical mask for 1 hour during treadmill exercise at 5.6 km/h vs the same exercise with no mask	N=20	60 min	Core temperature, cheek temperature, abdominal

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
					temperature, HR, RR, RPE, Perceived heat (RHP)
Scarano 2020	Two-period self-controlled trial	Wearing a surgical mask for 1 hour vs wearing N95 respirator for 1 hour vs baseline	N=20	60 min	Humidity, heat, breathing difficulty, discomfort, mask touching, perioral temperature
Shenal 2012	Multiple cross-over self-controlled field trial	Wearing one of seven respirators or medical mask during an 8-hour working period vs no mask	N=27	480 min	Discomfort, RPE
Tong 2015	Two-period self-controlled trial	Breathing through N95 mask materials during rest and exercise of predetermined intensity vs breathing ambient air	N=19	50 min	Oxygen consumption (VO2), carbon dioxide production (VCO2), VT, RR, VE, expired oxygen (FeO_2), expired carbon dioxide ($FeCO_2$), inspired oxygen (FiO_2), inspired carbon dioxide ($FiCO_2$)

Legend:
AT, anaerobic threshold; DBP = diastolic blood pressure; $EtCO_2$ = end-tidal CO_2 partial pressure; ESRD = end stage renal disease; TEWL= trans-epidermal water loss; FEV1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; HCW = health care worker; HD=haemodialyis; HR = heart rate; MEP = maximal expiratory pressure, TMET1 = metabolic equivalent; MIP =maximal inspiratory pressure; PEF = peak expiratory flow; PetCO2 = end-tidal carbon dioxide pressure; PetO2 =end-tidal oxygen pressure ; PI = perfusion index; PPE = personal protective equipment; $PtCo_2$ = partial transcutaneous CO_2 pressure; RER = respiratory exchange ratio; RPE = rated perceived exertion; RR = respiratory rate; RR =respiratory rate; SaO_2 =hemoglobin oxygen saturation; SBP = systolic blood pressure; SpO_2 = oxygen saturation; Te= expiratory time; Ti = inspiratory time; Ttot =Inspiratory + expiratory time; TV = tidal volume; V˙CO2 =carbon dioxide production; V˙O2 = oxygen uptake; VE = ventilation in liters/min; VE = ventilation; VT = tidal volume,

Table 1C: Included 31 observational studies

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
Beder 2008	Longitudinal and prospective observational study	Wearing surgical mask during major operations vs baseline	N=53	60-240 min	SpO_2,(oxygen saturation) HR (heart rate)
Choudhury 2020	Prospective cohort study	Wearing N95 respirator during light work vs wearing full PPE during heavy work vs baseline	N=75	240 min	HR,SpO_2, Perfusion Index (PI), RPE (rated perceived exertion), modified Borg scale for dyspnoea
Foo 2006	Survey study	Self-administered questionnaire healthcare workers	N=322	480 min	Prevalence of adverse skin reactions
Forgie 2009	Cross-sectional survey study	Self-administered questionnaire	N=80	Not given	Mask/Shield preference Mask results, Shield resul
Heider 2020	Cross-sectional survey study	Validated Voice Handicap Index (VHI)-10 questionnaire and self administered questionnaire	N=221	480 min	Vocal symptoms, Spanish validated Voice Handicap Index (VHI)-10 questionnaire
Islam 2022	Prospective cross-over self-control	Wearing FFP2 (N95) mask for 30 mins under sitting condition in	N = 10	30 min	Saha Institute of Nuclear

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
	study	an air-conditioned room			Physics, Department of Atomic Energy, Government of India
Jafari 2021	Cross-sectional study	Self-administered questionnaire, SpO2, HR and venous blood samples	N=243	240 min	RR, HR, SpO_2, salivary metabolic signature
Kao 2004	Prospective observational study	Wearing N95 respirator during haemodialysis vs baseline	N=39	240 min	HR, RR, systolic blood pressure (SBP), diastolic blood pressure (DBP), PaO_2, $PaCO_2$ discomfort rates
Klimek 2020	Cross-sectional Survey study	Visual Analogue Scales (VAS) to document patient-reported symptoms and diagnostic findings	N=46	120 min	Visual Analogue Scales (VAS) to document patient-reported symptoms of: rhinitis, rhinorrhea. Mucosal irritation, secretion and edema in nasal endoscopy was graded
Kyung 2020	Prospective panel study	Wearing N95 respirator during 6 minute walking test vs baseline	N=97	6 min	SBP, DBP, HR, RR, $EtCO_2$, SpO_2,
Lan 2020	Cross-sectional Survey study	Self-administered questionnaire	N=542	360 min	Prevalence of adverse skin reactions
Li 2005	Prospective observational study	Exercise on a treadmill while wearing the protective facemasks	N=10	100 min	HR, temperature and humidity (outside and inside the facemask), SBP, DBP, mask outer humidity, face microclimate humidity, chest microclimate humidity, mask outside temperature, face microclimate temperature, face skin temperature, chest microclimate temperature, subjective sensations: humiditty, heat, breath resistance, itching, tightness, feeling salty, feeling unfit, feeling odorous, fatigue, overall discomfort
Lim 2006	Survey study	Self-administered questionnaire	N=212	240 min	Prevalence of headaches
Luckman 2020	survey study using online experimental setting	Self-administered questionnaire and experimental online setting	N=400	Not given	Risk compensation with reduced physical distancing (standing, sitting, walking)
Matusiak 2020	Cross-sectional	Self-administered questionnaire	N=876	Not	Difficulty in breathing,

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
	Survey study			given	warming/sweating glasses misting up, slurred speech, itch
Mo 2020	Retrospective observation cross over cohort study	Wearing surgical mask vs not wearing: compare to former hospiatlisations. Including criteria: Patietns who were hospitalized three or more times and atr least two times before mask mandates	N=23	7 min	Vital signs: temperature, HR, RR, SBP, DBP, serum and blood gas analysis, inpatient days (days).clinical parameters, including ion concentration of serum, vital signs, inflammation markers and artery blood gas.
Naylor 2020	Survey study	Self-administered online questionnairess.	N=129	Not given	Effects of certain aspects of lockdown, including face masks, social distancing, and video calling, on participants behavior, emotions, hearing performance, practical issues, and tinnitus.
Ong 2020	Cross-sectional survey study	Self-administered questionnairee.	N=158	360 min	PPE usage patterns, occupation, underlying comorbidities
Park 2020	Prospective cohort study	Wearing KF94 respirator for 6 hours vs baseline	N=21	360 min	Skin temperature increase, skin redness, skin hydration, sebum level, skin elasticity, trans-epidermal water loss
Pifarre 2020	Prospective trial	No mask baseline vs. Mask baseline. Subjects wearing a mask immediately after a 21-flex test performed the Ruffier protocol	N=8	5-7 min	PaO_2, PaCO2, SpO2, HR
Prousa 2020	Cross-sectional survey study	Self-administered questionnaire	N=1010	Not given	Wearing time, discomfort Stress, Tricks, psychovegetative complaints, positive feelings, agression, depression
Ramirez-Moreno 2020	Cross-sectional study in healthcare workers	Self-administered questionnaire	N=306	420 min	Work type, type of face mask, number of hours worn per day (SD). pre-existing headache, comorbidity, other symptoms, Sleep disturbance, loss of concentration, irritability, photophobia, sonophobia, sickness/vomiting
Rebmann 2013	Multiple cross-over, self-control trial	Wearing only an N95 or an N95 with mask overlay for a 12-hour	N=10	720 h	SBP, DBP, CO_2 saturation,

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
		shift vs baseline			SpO_2, HR, headache, nausea, light-headedness, visual challenge
Rosner 2020	Cross-sectional study in healthcare workers	Self-administered questionnaire	N=343	360 min	Acne, headache, skin breakdown (nose bridge, cheeks, chin. behind ears), impaired cognition
Sukul 2022	Two-period controlled trial	Wearing a scurgical or N95 mask during rest (young to mid-aged adults were measured for 30 min and older adults were measured for 15 min)	N=30	15-30 min	Exhaled breath profiles within mask space by high-resolution real-time mass-spectrometry (PTR-ToF-MS): aldehydes, hemiterpene, organosulfur, short-chain fatty acids, alcohols, ketone, aromatics, nitrile and monoterpene. Haemodynamic parameters: SpO2, PETCO2, HR, RR, SBP, DBP, cardiac ouput,, exhaled oxygen, humidity.
Szczesniak 2020	Survey study	Self-administered online questionnaire After mask restrictions vs before mask restrictions	N=1476 vs 564	Not rgiven	Employment status, place of residence, worktime per week, somatic symptoms, anxiety and insomnia, aocial dysfunction, depression
Szepietowski 2020	Survey study	Self-administered online questionnaire	N=2307	Not given	itch, mask types used, duration of mask use per day
Techasatian 2020	Prospective cross-sectional survey study	Self-administered questionnaire	N=833	480 min	Factors associated with adverse skin reaction, risk factors for adverse skin reaction, differences between HCW and non-HCW
Thomas 2011	Two-period controlled trial	Comparing the ability to accurately record 20 randomized aviation terms transmitted over the radio by a helicopter emergency medical services (HEMS) pilot wearing a surgical facemask and six different N95s with and without the aircraft engine operating	N=3	Not given	Accurately record 20 terms transmitted over the radio by (HEMS) pilot wearing a surgical facemask or N95 mask
Toprak 2021	Prospective observational study	surgical vs N-95 mask n=149 vs n=148	N=297	35 min	Maternal vital signs: SBP, DBP, HR, RR, fever centigrade, SpO_2
Tornero-Aguilera 2021	Two-period controlled trial	Wearing a surgical facemask vs not wearing a facemask during 150 min university lessons	N=50	150 min	Mental fatigue perception, reaction time (ms) SpO2, mean RR (ms), mean HR

Author and year	Study design	Intervention/control	Sample size	Time	Outcomes
					(bpm) square root of the mean value of the sum of squared differences of all successive R-R intervals (RMSSD) (ms), low frequency (LF) and high-frequency (HF) normalized units (n.u.), SD1 (ms), SD2 (ms)

Legend:
AT, anaerobic threshold; DBP = diastolic blood pressure; $EtCO_2$ = end-tidal CO_2 partial pressure; ESRD = end stage renal disease; TEWL= trans-epidermal water loss; FEV1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; HCW = health care worker; HD=haemodialyis; HR = heart rate; MEP = maximal expiratory pressure, TMET1 = metabolic equivalent; MIP =maximal inspiratory pressure; PEF = peak expiratory flow; PetCO2 = end-tidal carbon dioxide pressure; PetO2 =end-tidal oxygen pressure ; PI = perfusion index; PPE = personal protective equipment; $PtCo_2$ = partial transcutaneous CO_2 pressure; RER = respiratory exchange ratio; RPE = rated perceived exertion; RR = respiratory rate; RR =respiratory rate; SaO_2 =hemoglobin oxygen saturation; SBP = systolic blood pressure; SpO_2 = oxygen saturation; Te= expiratory time; Ti = inspiratory time; Ttot =Inspiratory + expiratory time; TV = tidal volume; V˙CO2 =carbon dioxide production; V˙O2 = oxygen uptake; VE = ventilation in liters/min; VE = ventilation; VT = tidal volume,

Quality appraisal

The quality of the studies was not very homogeneous. The quality assessment identified some studies with low and average quality, which were excluded from the meta-analysis. We included only high-quality studies in our meta-analysis of RCT´s and nRCT. The quality of the included observational studies is predominantly good. Table 2 A-D summarises the results of the quality appraisal of the included research papers.

Mask type

Of the 37 meta-analytically evaluated studies, 31 examined the N95 mask, 19 the surgical mask with 1 not reporting on the specific type of mask due to the predominantly psychological research topic. There were 14 Studies evaluating both mask types (surgical and N95) and we compared the results in a separate meta-analysis (see below, Meta-analysis of N95 mask vs surgical mask).

Participants and time

8641 subjects were used to conduct the meta-analysis totalling 22127 individual measurements/surveys.
This population consisted of young (age=34.8±12.5) and predominantly female subjects (m=2482, f=6159).
Physiological, physical and biochemical data was used in the meta-analyses comprising of 934 participants and 3765 experimental measurements.
The pooled prevalence data was drawn from a study population of n=8128 and included 17383 data entries.
Most of the 37 studies, evaluated in meta-analyses included healthy participants. Twelve studies were conducted in health care workers (32%).
Two studies (5%) included chronic obstructive pulmonary disease (COPD), one study on haemodialysis patients, another study included children (3%) and 4 studies involved pregnant women (11%).
The median experimental time of the studies included in the meta-analyses (mostly controlled trials) on physiological, physical, and chemical face mask effects was 18 minutes with an interquartile range (IQR) of 50 minutes (min.: 6 minutes, max.: 360 minutes). There was a major deviating mask exposure duration with exceptions (mean of 45.8 minutes with a standard deviation of 69.9 minutes). Therefore, the mean was not an appropriate parameter to characterise this distribution).
The study with the longest experimental duration (360 minutes, observational) included only 21 healthy participants, which corresponds to 2.2% of the total population studied (n=934).
Interestingly, the studies on symptoms (including many observational studies) had significantly longer observation times and a mean of 263.8±170.3 minutes (median 240, IQR 180) in a total of n=8128 participants.

Table 2 A-D: Summary of the quality appraisals for the included studies. Part A shows the quality analysis of RCTs with Cochrane RoB tool++, while Part B lists the results of the quality analysis of nRCTs with CASP checklist. Part C is on the quality analysis of observational (non questionnaire) studies with CASP checklist. Part D documents the quality analysis of the questionnaire studies by means of a similar checklist.

Table 2 A: Quality appraisal of randomised controlled trials

Publication	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	
	1. Random Sampling	2. Allocation Blinding	3.Blinding for Intervention	4. Evaluation Blinding	5. Incomplete Data	6. Selective Reporting	7. Other Bias
Bertoli 2020	LR	LR	HR	HR	LR	UC	LR
Butz 2005	LR	LR	HR	LR	UC	UC	UC
Dirol 2021	LR	LR	HR	LR	LR	LR	LR
Fikenzer 2020	LR	LR	HR	LR	LR	LR	LR
Georgi 2020	LR	LR	HR	LR	LR	UC	LR
Goh 2019	LR	LR	HR	LR	LR	LR	LR
Hua 2020	LR	LR	HR	LR	UC	UC	LR
Kim J.H. 2013	HR	LR	HR	LR	LR	LR	LR
Kim J.H. 2015	LR	LR	HR	LR	LR	UC	LR
Kim J.H. 2016	LR	LR	HR	LR	LR	UC	LR
Mapelli 2021	LR	LR	HR	LR	LR	UC	LR
Roberge 2014	LR	LR	HR	LR	LR	UC	LR
Wong A.Y.-Y 2020	LR	LR	HR	LR	LR	UC	LR
Zhang 2021	LR	LR	HR	LR	LR	LR	LR
Legend: LR=low risk, HR=high risk, UC=Unclear							

Table 2 B: Quality appraisal of non-randomised controlled trials

Publication	**1. clear focus?**	**2. appropriate methods?**	**3. recruitment comprehensible?**	**4. valid measurement of exposure?**	**5. valid measurement of outcome?**	**6. equality of groups?**	**7. confounders taken into account?**	**8. sufficient size and significance of the effect?**	**9. credibility of the results?**	**10. transferability to other populations? clear focus?**	**11. comparability with existing evidence?**
Bharatendu 2020	Y	Y	Y	Y	UC	Y	Y	Y	UC	Y	UC
Coniam 2005	UC	N	Y	Y	Y	UC	UC	Y	Y	Y	UC
Epstein 2021	Y	Y	Y	Y	Y	Y	UC	N	Y	Y	Y
Lee 2011	Y	Y	Y	Y	N	Y	Y	N	UC	Y	UC
Roberge 2012	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Roberge 2010	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Scarano 2020	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	UC
Shenal 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC
Tong 2015	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	UC
Legend: Y=Yes, N=No, UC=Unclear											

Table 2 C: Quality Appraisal of the Observational Studies

Publication	1. clear focus?	2. appropriate methods?	3. recruitment comprehensible?	4. valid measurement of exposure?	5. valid measurement of outcome?	6. equality of groups?	7. confounders taken into account?	8. sufficient size and significance of the effect?	9. credibility of the results?	10. transferability to other populations? clear focus?	11. comparability with existing evidence?
Beder 2008	Y	Y	N	Y	Y	UC	N	Y	Y	Y	Y
Choudhury 2020	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
Islam 2022	Y	Y	Y	Y	Y	Y	UC	Y	UC	Y	Y
Jafari 2021	Y	Y	Y	Y	Y	Y	UC	Y	Y	N	UC
Kao 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	UC
Klimek 2020	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	UC
Kyung 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	UC
Li 2005	Y	Y	Y	Y	Y	Y	Y	UC	Y	Y	UC
Luckman 2020	Y	UC	N	Y	Y	Y	Y	Y	Y	Y	UC
Mo 2020	Y	Y	Y	Y	Y	UC	UC	Y	Y	Y	Y
Park 2020	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	UC
Pifarre 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC
Rebmann 2013	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y
Sukul 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC
Thomas 2011	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	UC
Toprak 2021	Y	Y	Y	Y	Y	UC	N	Y	Y	N	Y
Tornero-Aguilera 2021	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Legend: Y=Yes, N=No, UC=Unclear											

Table 2 D: Quality Appraisal of the Questionnaire Studies

Publication	Study design	Validity and reliability		Questionnaire quality		Questionnaire design		Sample	Distribution and response			Analysis	Results			Summary and recommendation	
	Was a questionnaire study an appropriate method?	Are the results valid and realistic?	Does the questionnaire used provide reliable results?	Were sample questions provided?	Are the questions formulated in a clear and understandable way?	Details on how the questionnaire was prepared?	Was the questionnaire prepared in an appropriate manner?	Was the sample sufficiently large and representative?	Was information provided on how the questionnaire was made available?	Was information provided on response rates and exclusion criteria?	Was potential response bias discussed?	Were the results analysed appropriately?	Were all relevant results published?	Were both significant and non-significant results published?	Were results adequately interpreted?	Does the summary reflect the results of the study?	Were the results placed in context with existing literature?
Foo 2006	Y	Y	UC	N	UC	N	UC	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Forgie 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	UC	Y	N	Y	Y	Y
Heider 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lan 2020	Y	Y	UC	N	UC	N	UC	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Lim 2006	Y	Y	UC	N	UC	N	UC	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Matusiak	Y	Y	UC	N	UC	Y	Y	Y	Y	Y	N	Y	UC	Y	Y	Y	Y

2020																	
Naylor 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ong 2020	Y	Y	UC	N	UC	N	UC	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Prousa 2020	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	N	Y	UC
Ramirez 2020	Y	Y	UC	N	UC	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Rosner 2020	Y	Y	UC	N	UC	N	UC	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Szczesniak 2020	Y	N	UC	N	UC	N	UC	Y	Y	N	N	Y	UC	N	N	Y	Y
Szepietowski 2020	Y	Y	UC	N	UC	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Techasatian 2020	Y	Y	UC	N	UC	N	UC	Y	Y	N	N	Y	Y	Y	Y	Y	Y
	Study design	Validity and reliability		Questionnaire quality		Questionnaire design		Sample	Distribution and response			Analysis	Results			Summary and recommendation	
Legend: Y=Yes, N=No, UC=Unclear																	

Qualitative evaluation

Of the 54 included studies, 51 reported numerous adverse mask effects across multiple clinical disciplines, as already compiled in a previous scoping review [8]. Also fourteen of the 17 studies, which were not included in the meta-analysis reported those numerous mask effects.
Overall, our systematic review found mask related symptoms that can be classified under the previously described Mask-Induced Exhaustion Syndrome (MIES) [8], with typical changes and symptoms that are often observed in combination.
Among the included 54 studies (Table 1), we detected and compiled reports on frequently statistically significant physiological and psychological changes ($p<0.05$) belonging to the MIES such as:

-i*ncrease in breathing dead space volume*[43,44]
-*increase in breathing resistance* [45–49]
-*increase in blood carbon dioxide* [20,43–45,50–64]
-*decrease in blood oxygen saturation* [20,44,45,48,49,52,53,55,56,58,60,61,63–68]
-*increase in heart rate* [20,44,47,49,52,56–58,61,62,65,67–69]
-*decrease in cardiopulmonary capacity* [45,48,64]
-*changes in respiratory rate* [44,45,48,52,53,57,58,62,64,66,67]
-*shortness of breath and difficulty breathing* [41,45,47,52,53,55,58,59,61,61,62,66,70–73]
-*headache* [50,53,61,70,72,74–78]
-*dizziness* [53,58,66]
-*feeling hot and clammy* [44,45,47,52,55,62,71,73]
-*decreased ability to concentrate* [68]
-*decreased ability to think* [58,61,68,78]
-*drowsiness* [78]
-*impaired skin barrier function* [41,78,79]
-*itching* [45,41,47,52,71,79–83,75]
-*acne, skin lesions and irritation* [79,41,58,71,62,78,82,75]
-*false sense of security* [84,85]
-*overall perceived fatigue and exhaustion* [70,52,45,53,66,55,56,47,48,44,62,86,63,69,64,61].

Moreover, we could objectify additional symptoms of the MIES as follows:

-d*ecrease in ventilation* [45,48,64]
-*increase in blood pressure* [20,45,47,48,52,58,59,64,67]
-*increase of measured temperature of the skin under the mask* [55,62,73,87]
-*increase of measured humidity of the air under the mask* [55,73,87]
-c*ommunication disturbance* [61,71,78,88,89]
-v*oice disorder* [71,90]
-*perceived discomfort* [41,45,52,73]
-*increased anxiety* [72,88,91]
-*increased mood swings or depressive mood* [72,88,90,91]

and:

-*changes in microbial metabolism* [20,92]

However, three studies (6% of the included papers) describe the absence of adverse or even positive mask effects [85,93,94].

Results of the meta-analysis

In the meta-analytic evaluation, we found biochemical, physiological, physical, and perceptual symptoms with face mask use. We were also able to meta-analyse the pooled prevalence of symptoms. These results are presented in detail below.

Meta-analysis of biochemical effects of face masks

SpO_2 and face masks

The results are summarised in Figure 2A.
In a pooled analysis, blood oxygen saturation is significantly lowered during mask use. This could be found for general mask use (p=0.0004, SMD= -0.24, 95% CI -0.38 to -0.11, Z=3.53, I^2=0%). The Eggers' test does not indicate the presence of funnel plot asymmetry (t(df=11)=-0.70, p=.50). This was also confirmed in the subgroup analysis for N95 mask use (p=0.001, SMD= -0.3, 95% CI -0.49 to -0.12, Z=3.19, I^2=0%), but not for surgical mask use (p=0.08, SMD= -0.17, 95% CI [-0.37; 0.02], Z=1.77, I^2=0%). However, 7 of 9 studies in the N95 mask meta-analysis contain the "0" in the confidence interval and are not significant because of n being too small (sample size). From the pooled analysis, it seems that N95 mask use may be responsible for a larger SpO_2 drop than surgical masks.
In a separate meta-analysis of pre-post studies an equally significant drop in SpO_2 was found when using a mask (p=0.0001, SMD= -1.24, 95% CI -1.87 to -0.61, Z=3.87, I^2=80%) especially in the subgroup of N95 masks (p=0.02, SMD= -1,24, 95% CI -2.26 to -0.22, Z=2.37, I^2=89%), yet with a high heterogeneity.

Blood CO_2 content and face masks

The results are summarised in Figure 2B.
In a pooled analysis, blood carbon dioxide content was found to be significantly elevated in mask use. This was perceived for general mask use (p=0.0001, SMD=0.64, 95% CI 0.31 to 0.96,Z=3.86, I2=81%). The Eggers' test does not indicate the presence of funnel plot asymmetry (t(df=11)=-0.87, p=.40). This was also confirmed for N95 mask use (p=0.003, SMD=0.78, 95% CI 0.28 to 1.29,Z=3.02, I^2=84%) and also for surgical mask use (p<0.00001, SMD=0.42, 95% CI 0.24 to 0.59, Z=4.65, I^2=0%).
There was no significant difference between the pooled effect sizes of N95 and surgical masks (Q(df=1)=3.09, p=.08). Further separate pooled evaluations were also carried out for $PtCO_2$, $ETCO_2$ and $PaCO_2$, for each surgical and N95 masks with a significant increase in blood CO_2 with predominantly low heterogeneity.
Even in a separate meta-analysis of pre-post studies with high heterogeneity, a significant increase in blood carbon dioxide content was found when using a mask (p=0.003, SMD=1.44, 95% CI 0.49 to 2.39, Z=2.97,I^2=94%) and also in the subgroup of N95 masks (p=0.02, SMD=1.51, 95% CI 0.24 to 2.78, Z=2.34,I^2=96%).
Interestingly, 11 of 17 studies include "0" in the confidence interval and the majority showed no effect. The studies that showed clear effects (not including 0 in their confidence interval) differed from those that showed no certain effects as they either included N95 and/or pregnant women or children. The study by Dirol et al is an exception but has a sample size of n=100 for surgical masks. Apparently, it takes N95 masks and vulnerable populations or appropriately large samples in surgical masks to make the effects more quantifiable and precise.

Accordingly, in the surgical mask meta-analysis, studies that included "0" in the confidence interval were of small sample size, with a mean of n=24 and a median of n=14. The advantage of a meta-analysis is to combine several imprecise effects into a more precise overall effect [30].

Meta-analysis of physiological effects of face masks

Ventilation(V_E) in L/min and face masks

The results are summarised in Figure 3A.
Despite compensatory mechanisms, breathing volume (L/min) is significantly lowered during mask use in the pooled analysis.
This was not only verified for general mask use (p<0.00001, SMD= -0.72, Z=5.36, 95% CI -0.99 to -0.46, I^2=0%) in studies evaluated with an overall low heterogeneity (I^2=0), but also for surgical (p<0.0001, SMD= -0,54, 95% CI -0.94 to -0.35, Z=4.32, I^2=0%) and N95 mask use (p=0.0007, SMD= -1.06, 95% CI -1.68 to -0.45, Z=3.39, I^2=0%). Both studies had an overall low heterogeneity(I^2=0).
On average, masks reduce respiratory minute volume by -19% according to our meta-analysis, and by as much as -24% for N95 masks; the difference between surgical and N95 masks is -10% respiratory minute volume.

Respiratory rate and face masks

The results are summarised in Figure 3B.
Interestingly, no statistical difference regarding respiratory rate was determined in mask use in the pooled analysis.
Even in the subgroups containing N95 and surgical masks, no difference compared to the no mask condition could be found.

Systolic blood pressure (SBP) and masks

The results are summarised in Figure 4A.
A significant elevation in systolic blood pressure was found for mask users with p=0.02, SMD= 0.17, 95% CI 0.03 to 0.32, Z=2.39 and I^2=0% in the pooled analysis. It is a small effect and in 9 out of 10 studies insignificant, including 2 with higher n in each case. The Eggers' test does not indicate the presence of funnel plot asymmetry (t(df=8), p=.27). This was verified in the subgroup analysis for surgical masks (p=0.02, SMD= 0.21, 95% CI 0.03 to 0.39, Z=2.33, I^2=0%). In studies evaluating both mask types (surgical and N95) the N95 mask always yielded a higher SBP than the surgical mask. However, this effect was not statistically significant. There is no significant difference between the pooled effect sizes of N95 and surgical masks (Q(df=1)=0.98, p=.32).

Heart rate and masks

The results are summarised in Figure 4B.
No statistically significant difference regarding the heart rate during mask use was found in the pooled analysis. The Eggers' test does not indicate the presence of funnel plot asymmetry (t(df=14), p=.94). However, in the subgroup analysis containing surgical and N95 masks, only for the N95 mask condition a weak significance for a slight increase in heart rate could be found (p=0.02, SMD= 0.22, 95%CI 0.03 to 0.41, Z=2.30 and low heterogeneity of studies with I^2=0). There is no significant difference between the pooled effect sizes of N95 and surgical masks (Q(df=1)=1.26, p=.26).

Meta-analysis of physical effects of face masks

Skin temperature and face masks

The results are summarised in Figure 5A.
Skin covered by mask has a significantly higher temperature during rest and activity. This could be found for general mask use (p=0.005, SMD=0.80, 95% CI 0.23 to 1.38, Z=2.81. I^2=72%), for N95 mask use (p=0.02, SMD=0.72, 95% CI 0.12 to 1.32, Z=2.35, I^2=55%), but not for surgical mask use (p=0.21, SMD=0.96, Z=1.26, I^2=90%).

Humidity and face masks

The results are summarised in Figure 5B.
The dead space covered by mask has a significantly higher humidity in the pooled analysis.
This could be found for general mask use with p<0.00001, SMD=2.24, 95% CI 1.32 to 3.17, Z=4.75 and I^2=50%).

Meta-analysis of measured symptoms and sensations during face mask use

Discomfort and face masks

The results are summarised in Figure 6A.
Perceived discomfort is significantly higher in mask use during rest and activity in the pooled analysis.
This could be found for general mask use (p<0.0001, SMD=1.16, 95% CI 0.58 to 1.73, Z=3.94, I^2=74%), for N95 mask use (p<0.00001, SMD=1.98, 95% CI 1.37 to 2.59, Z=6.34, I^2=0%) as well as for surgical mask use (p<0.00001, SMD=0.71, 95% CI 0.46 to 0.96, Z=5.58, I^2=0%).

Itch and face masks

The results are summarised in Figure 6B.
In N95 mask use, the perceived itching was significantly elevated (p=0.003, SMD=2.65, 95% CI 1.21 to 4.09, Z=3.6, I^2=83%) during activity according to the pooled subgroup analysis.
Although not statistically significant, an overall tendency for itching was found for general mask use in the pooled analysis.

Exertion and face masks

The results are summarised in Figure 6C.
Perceived exertion is significantly higher in mask use during activity in the pooled analysis.
This could be found for general mask use (p<0.0001, SMD=0.90, 95% CI 0.58 to 1.23, Z=5.31. I^2=71%), for N95 mask use (p=0.002, SDM=1.19, 95% CI 0.43 to 1.95, Z=3.06, I^2=81%) as well as for surgical mask use (p<0.0001, SMD=0.63, 95% CI 0.40 to 0.87, Z=5.29, I^2=24%). The Eggers' test indicates the presence of funnel plot asymmetry (t(df=10)=2.68, p=.02). For N95 mask use (p=0.002, SDM=1.19, Z=3.06, I2=81%) and this result was confirmed for surgical mask use too (p<0.0001, SMD=0.63, Z=5.29, I2=24%). There is no significant difference between the pooled effect sizes of N95 and surgical masks (Q(df=1)= 1.97, p=.16).

Shortness of breath and face masks

The results are summarised in Figure 6D.
Perceived shortness of breath is significantly higher during mask use during activity in the pooled analysis (p=0.006, SMD=1.46, 95% CI 0.42 to 2.50, Z=2.75, I^2=86%).
In the subgroup analysis for surgical and N95 masks, the masks always led to an increase in perceived shortness of breath, but the number of studies that could be included was very limited and no statistically significant results were found in the subgroup analysis.

Perceived heat and face masks

The results are summarised in Figure 6E.
Perceived heat is significantly higher during mask use with physical activity in the pooled analysis (p=0.002, SMD=0.70, 95%CI 0.28 to 1.13, Z=3.27, I^2=62%).
In the subgroup analysis containing surgical and N95 masks the heat perception was increased in both mask types, but only for the surgical mask condition a statistical significance for an increase in heat perception could be found (p=0.008, SDM=0.61, 95% CI 0.16 to 1.06, Z=2.66, I^2=50%).

Perceived humidity and face masks

The results are summarised in Figure 6F.
Perceived humidity is significantly higher in mask use during activity according to the pooled analysis (p=0.002, SMD=0.90, 95% CI 0.34 to 1.46, Z=3.17, I^2=53%).
The subgroup analysis containing surgical and N95 masks was completed merely for surgical masks due to lack of studies on N95 masks.
In the surgical mask condition a statistical significance for an increase in humidity perception could be found (p<0.00001, SMD=0.63, 95% CI 0.36 to 0.90, Z=4.6, I^2=0).

Meta-analysis of N95 mask vs surgical mask

The results are summarised in Figure 7A-C.
The N95 mask leads to measurably worse effects compared to the surgical mask. The blood oxygenation is significantly decreased when using a N95 mask compared to a surgical mask with p=0.003, SMD= -0.53, 95%CI -0.88 to -0.18, Z=2.98, I^2=37%. The heart rate (p=0.01, SMD=0.25, 95% CI 0.05 to 0.45, Z=2.47, I^2=0%), the perception of discomfort (p=0.02, SMD=3.07, 95% CI 0.52 to 5.61, Z=2.36, I^2=95%) and humidity (p=0.02, SMD=0.59, 95% CI 0.09 to 1.10, Z=2.32, I^2=0%) increased in each case when the N95 mask was compared to the surgical mask. This trend was also evident for CO_2, minute volume, exertion, heat, shortened breath and systolic blood pressure, but was not statistically significant due to the limited available studies.

Meta-analysis with pooled prevalence of symptoms during face mask use

The results are summarised in Figure 8.
The prevalence of headaches with mask use is significant in the majority of evaluated users (n=2525), with a pooled prevalence of 62% (p<0.00001, 95%CI 0.48 to 0.75) and even 70% (p<0.00001, 95%CI 0.52 to 0.88) with N95 mask use.
Acne when using a mask is significantly present in evaluated users (n=1489) with a pooled prevalence of 38% in general mask use (p<0.00001, 95%CI 0.22 to 0.54).
Skin irritation occurrence when using a mask is significantly present in the evaluated users (n=3046) with a pooled prevalence of 36% in general mask use (p<0.00001, 95%CI 0.24 to 0.49).

Shortness of breath rate when using a mask is significantly present in users (n=2134) with a pooled prevalence of 33% in general mask use ($p<0.00001$, 95%CI 0.23 to 0.44) and 37% in N95 mask use ($p=0.01$, 95%CI 0.07 to 0.67).
The prevalence of itch with mask use is substantial in evaluated users (n=5000), with a pooled prevalence of 26% ($p<0.00001$, 95%CI 0.15 to 0.36). In the subgroup analysis, the pooled prevalence for itch in N95 mask use was 51% ($p<0.00001$, 95%CI 0.47 to 0.55) while it was 17% in surgical mask use ($p<0.0001$, 95%CI 0.09to 0.26). These results were confirmed in control calculations using the R software.
The prevalence of voice disorders when using a mask is significant in evaluated users (n=1097) with a pooled prevalence of 23% in general mask use ($p=0.03$, 95%CI 0.02 to 0.43), however with high heterogeneity of the included studies.
The prevalence of dizziness when using a mask is significant in evaluated users (n=153) with a pooled prevalence of 5% in general mask use ($p=0.01$, 95%CI 0.01 to 0.09). Due to the small sample size (n) in the referred studies, there are wide confidence intervals. This results in a significant, but not really pronounced overall result for dizziness.

Discussion

Besides the anticipated protection against the transmission of pathogens, face masks undoubtedly impede natural breathing. Such respiratory impairments due to the “new-normal” lifestyle under the present global pandemic have imposed potential adverse effects on our usual external and internal respiration, affecting a wide range of physio-metabolic processes within various organ systems and/or at cellular levels [8,20]. Ensuing consequences were eventually observed at the physical, psychological and social levels along with certain clinical symptoms in the individual human being [8]. In this systemic review, we applied meta-analysis and comprehensive evaluations of physio-metabolic, physical, psychological and clinical burdens of wearing face masks in the general population. Restricting breathing through face masks has turned out to be a fundamental, incisive intervention with possible negative effects on public health.

Physio-metabolic burden of masks

Our meta-analysis clearly depicts that masks significantly restrict O_2 uptake and hinder CO_2 release. Based on the meta-analytic effect sizes defined by Cohen [95], the effect size for CO_2 retention (as per $PtCO_2$, $ETCO_2$ and $PaCO_2$ outcomes) is medium for all mask types and is larger for N95 masks. The effect size for O_2 uptake disturbance (as per SpO_2 outcome) is relatively smaller but highly significant ($p=0.0004$) (Fig. 9A and Fig. 2 A, B). Such respiratory gas-exchange discrepancy can be attributed to the constantly increased dead space ventilation volume [8,43,44,96,97] (i.e., continuous rebreathing from the masks dead space volume) and breathing resistance [8,45–49]. Continuous CO_2 rebreathing causes the right-shift of haemoglobin-O_2 saturation curve. Since O_2 and CO_2 homeostasis influences diverse down-stream metabolic processes, corresponding changes towards clinically concerning directions may lead to unfavourable consequences such as transient hypoxaemia and hypercarbia, increased breath humidity and body temperature along with compromised physiological compensations etc..

Transient hypoxaemia

A progressive decrease in SpO_2 is observed with respect to the duration of wearing a mask [20,52,55,57,58,60,65,70,98]. The decline in SpO_2 levels confirmed in our systemic-review supports the onset and progression of oxidative stress (via significantly increased exhaled breath aldehydes – originating from lipid peroxidation) reported by Sukul et al [20]. Studies have shown that oxidative stress (under hypoxic conditions) can inhibit cell-mediated immune response (e.g. T-lymphocytes, TCR CD4 complex etc.) to fight viral infections, which may gradually lead to immune suppression [99,100]. Arterial hypoxaemia increases the level of the hypoxia inducible factor-1α (HIF-1α), which further inhibits T-cells and stimulates regulatory T-cells [100]. This may set the stage for contracting any infection, including SARS-CoV-2 and making the consequences of that infection much more severe. In essence, masks may put wearers at an increased risk of infection and severity [99–101]. A recent review [102] by Serebrovska et al discusses a possible link between HIF-1α activation and cell entry of SARS-CoV-2. If the cell is already under oxidative stress, activation of HIF-1α may suppress important adaptive mechanisms e.g., autophagy or proteasomal proteolysis is leads to the induction of necrosis and excessive cytokine production. Sturrock et al [103] demonstrated that the SARS-CoV-2 receptor (e.g., ACE2 and TMPRSS2) expression by primary type II alveolar epithelial cells increased significantly following exposure to hypoxic environments *in vivo* and *in vitro*. Furthermore, recent research has demonstrated that the cellular entry of SARS-CoV-2 also depends on many other receptor paths/routes (e.g., CD147, CD147 - spike proteins etc.), mediated by HIF-1α upregulation [104–107]. Therefore, the effect of even mild hypoxaemia for an extended span may promote an infection risk along with metabolic stress e.g., due to altered pH via respiratory acidosis. In line with that, Sukul et al [20] observed a significant decrease in exhaled volatile metabolites (e.g. organosulfur and short-chain fatty acids) originating from the lower gut microbiota during face mask use – indicating anaerobiosis, metabolic acidosis and possible immunosuppression. Even marginal local effects of masks on salivary metabolites in young and healthy adults have indicated alteration of microbial metabolic activity [92].

The findings of Spira 2022 [10] from European data show that mask use correlates with increased morbidity and mortality, which could be due to the above-discussed possible processes. Moreover, prolonged hypoxic conditions and low oxygen levels pave the way for immunosuppression and inflammation, which can promote the growth, invasion and spread of cancers [107–109].

However, further experimental studies are needed to prove that hypoxaemia under long-term mask use may result in quantifiable changes in HIF-1α and immunosuppression – especially in elderly, ill/comorbid and/or immunocompromised individuals.

Transient hypercarbia

In line with the increased dead space ventilation and consistently decreasing SpO_2 level, CO_2 inhalation elevates progressively during the course of wearing a mask, causing transient hypercarbia [20,52,55,57,58,60,98]. Very recent experimental data exist on CO_2 concentrations of concern in the air breathed while wearing masks, especially in children [110,111]. Systemic CO_2 concentration exerts an important influence on the intra- and extracellular pH. CO_2 passes quickly through the cell membranes to form carbonic acid, which releases protons and in excess causes acidosis [112–114]. With a prolonged CO_2 burden the body uses the bones (CO_2 storage) to regulate the blood pH: bicarbonate and a positive ion (Ca^{2+}, K^+, Na^+) are exchanged for H^+. Accordingly, kidney and organ calcification were frequently seen in animal studies on low-level CO_2 exposure [115,116]. Additionally, CO_2 in relationship with chronic and/or intermittent long-term exposure might induce pathological states by favouring DNA alterations and inflammation [117,118]. Moreover, inflammation is reported to be caused by low-level CO_2 exposure in humans and animals [118–122]. Even slightly elevated CO_2 induces higher levels of pro-inflammatory Interleukin-1β, a protein involved in regulating immune responses, which causes inflammation, vasoconstriction and vascular damage [121]. In addition, carbon dioxide is also known as a trigger of oxidative stress caused by reactive oxygen species (ROS) [117] including oxidative damage to cellular DNA [117,118].

Altogether, the possible damaging mechanism of CO_2 affecting tissues is based on the conditions of oxidative stress and acidosis with increased inflammation and apoptosis as described above [117,119–124]. In the long term, therefore, this could be possible during mask use even at blood-CO_2 levels that do not reach the thresholds. In spontaneously breathing subjects in a sitting position, exhaled CO_2 profiles mirror the endogenous isoprene exhalation [12,125]. Significant and progressively decreased breath isoprene recently observed in adults [20] indicates the deoxygenation driven sympathetic vasoconstriction in the peripheral compartments [126]. Prolonged deoxygenation and CO_2 re-breathing therefore, may eventually lead to pulmonary vasoconstriction that may hinder blood-CO_2 levels to reach the thresholds. For instance, Sukul et. al also reported the presence of significant hyperventilation state in older adults aged ≥ 60 years before wearing a face mask for the participation in experiments. This indicates a compromised respiratory compensation of precedent mask use (which was obligatory due to pandemic regulations at that time) by these subjects.

Physical burden of masks: Humidity and skin temperature

Together with the immune-inhibiting mechanisms mentioned above, we found some other possible deleterious mask effects that contradict healthy natural breathing. The most prominent and extreme effect was found in the increase of air humidity and skin temperature within the dead space of the mask (Figure 9B and Figure 5). Increased humidity and temperature can increase droplet and aerosol generation, which facilitate liquid penetration through the mask mesh. This not only increases the chance of microorganism (fungal and bacterial pathogens) growth on and in masks [127–129] causing increased risk for accumulation of fungal and bacterial pathogens [127,129] including mucormycosis [130], but also leading to re-breathing of viruses that may be trapped and enriched within the moisturised mask meshwork. Therefore, these conditions within masks are favourable for pathogenic growth and are unfavourable for good/systemic microbiota i.e., individual specific. As a result, the isolation of people with masks for extended periods can attain conditions for new and individual specific strains formations/mutations of pathogens – to which other people in the environment will be susceptible and/or not immune. Additionally, the high concentration of microbiome in masks can be a potential source of infection for the population. The findings of Fögen 2022 [5] using data from the USA which shows that mask use correlates with an increased mortality could be due to these processes. This phenomenon could also explain the similar figures found by Spira [10] in the EU.

Compensatory physiological mechanisms

Our meta-analytically quantified CO_2-rise and O_2-depletion (Figure 2, 9A) with mask use certainly needs physiological compensations (Figures 3, 4 and 10). Interestingly, the compensatory responses to mask wearing (e.g., rise in heart rate, changes in respiratory rate and/or minute ventilation etc.) was lower (absent or even reverse) than expected [115,131,132]. In former human experiments with low level 1-2% CO_2 exposure to breathing air – which corresponds to measured values during mask use [133] – an increased respiratory minute volume (V_E) of >34% was detected [115]. In contrast to that and according to our results under masks a significantly decreased V_E by -19% on an average and up to -24% under N95 masks occurs despite face mask driven CO_2 exposure [133]. Even the V_E differed by 10% between N95 and surgical masks (Figure 3A). However, it appears to have no acute clinical impact in the short term and does not exceed normal values of SpO_2 and systemic CO_2 although these may become problematic in the long run. A compensatory higher arterial $PaCO_2$ and bicarbonate levels execute the buffering of inhaled CO_2. Interestingly, during chronic breathing of low CO_2 concentrations (in the no-mask condition), due to compensatory mechanisms, e.g. lowered blood pH, increased respiratory rate and V_E [115] and an acclimatisation occurs [115,131,132,134,135]. In mask users, those compensatory mechanisms however seem to differ or get disturbed (e.g. no rise in respiratory rate, heart rate and simultaneous fall in V_E). Health risks should be considered despite the mask related compensation attempts [133]. During face mask use a rise in the arterial $PaCO_2$ is possible in the long term [20,52,58,60,98]. Although, $PaCO_2$ generally remains at a sub-threshold level in

healthy mask users [98,131], concerning pathological changes can occur in older (>60 years) and sick people [20,59].
Our findings depicted an absence of typical compensatory reactions to transient hypercarbia thereby implying a suppression of a physiological response owing to the unusual conditions of wearing a mask. The reasons behind this phenomenon, i.e. the absence of a rise in the respiratory rate and ventilation, remain unclear. The simultaneous change in the adverse direction (CO_2 rise and simultaneous O_2 fall with concomitant dead space- and resistance enlargement caused by the mask) may be responsible for this. The drop in SpO_2 and the rise in CO_2 ($PtCO_2$, $ETCO_2$, $PaCO_2$) with no major changes in the heart rate in our meta-analysis also transpires to be an unexpected reaction. Sukul et al [20] reported altered breathing patterns, respiratory resistance and discomfort under medical masks. Adults younger than 60 years of age described slow breathing (slow and deep inspiration and expiration) under masks, whereas shallow/thoracic breathing (breathing with increased inhalation duration and effort), respiratory resistance and dyspnoea was portrayed by those ≥ 60 years of age. Fittingly, altered breathing patterns/kinetics, progressive changes towards deoxygenation, hypercarbia and insignificant changes in the respiratory and heart rate transpired to be surprising mask outcomes in our present results (hypercapnia-like effects). Thus, prolonged masks use may lead to hypercapnic hypoxia like conditions. While short and acute hypercapnic hypoxia like conditions in healthy individuals can promote positive effects (sport, training etc.), a chronic/prolonged hypercapnic hypoxia (as known from sleep apnoea) is toxic for the cardiovascular system in the long run – causing metabolic syndrome [8] as well as additional effects on cognitive functions [136].

N95 mask compared to surgical mask

In line with recent findings by Kisielinski 2021 [8] and Sukul 2022 [20], the present results clearly show that N95 masks lead to significantly more pronounced and unfavourable biochemical, physiological and psychological effects (Figure 7) than surgical masks. Altogether, the results in blood oxygenation, discomfort, heart rate, CO_2, exertion, humidity, blood pressure, V_E, temperature, dyspnoea and itching etc. can be attributed to the larger (almost doubled) dead space and higher breathing resistance of the N95 mask [8]. Compared to the surgical mask upon the short-term effects, N95 masks could impose elevated health risks under extended use. Interestingly, recent data from a large multi-country RCT study show no significant differences between the two mask types in terms of SARS-CoV2 infection rates [137].

Short mask experiment times

It is noteworthy to say that in studies with short assessment times neither correspond to real-life conditions nor do they exclude short-term compensatory mechanisms, e.g. obvious for CO_2-rebreathing. However, immediate compensatory mechanisms can hide further adverse reactions [115,131,133]. Therefore, longer observation times can lead to clearer values that are closer or above the thresholds due to the attenuation or collapse of transient physiological mechanisms. The experimental studies used here examined important outcomes only had a median examination time of 18 minutes (Figure 11). Heterogeneous studies with small sample sizes yielded significant and medium to strong results (Figures 10 and 12). Nevertheless, experimental studies with longer assessment periods are needed.
The observational studies included in the present analysis on symptoms were conducted over significantly longer periods (median 240 min, IQR 180) and are able to consider cumulative and long-term effects. It is known that observational studies are far more precise in finding negative effects and are particularly suitable to investigate exposures (e.g., air pollution or smoking) that are difficult or impossible to investigate in randomised controlled trials (RCTs). In addition,

observational studies are important to investigate causes with a long latency period, such as toxicological and carcinogenic effects from environmental exposures or drugs [42].
The longest period of included studies was 8 months with an averaged of wearing the mask 8 hours per day (observational study), however with the shortest study with a 5 minutes examining/exposition time (controlled trail).

Possible sub-threshold impact of masks –the low-dose long-term effect on health

In contrast to our study, most of the recent systematic reviews [21–25] have only analysed a few outcome threshold values without considering comprehensive effects, exposure time and the susceptibility of the exposed organisms and tissues. Therefore, their recommendations e.g. masks are harmless and safe for everybody etc. appears to be superficial, non-medical, non-holistic and misleading.
In accordance with conclusions of Fikenzer, Sukul and Zhang [20,45,64], we have found hints to deleterious effects even without exceeding physiological threshold values and we have interpreted these data as a risk for individuals with suppressed compensatory mechanisms such as in elderly and sick subjects with cardiorespiratory diseases, infection, diabetes, cancer and other comorbidities. Sukul et al [20] were able to show that the unfavourable effects are more pronounced in the elderly (aged: 60 – 80 years). Moreover, they could provide evidence for toxic effects of face masks including oxidative stress, immunosuppression, deoxygenation and hypercarbia induced vasoconstriction and altered systemic microbial activity. Even with CO_2 and SpO_2 levels that do not exceed the limits, many clinical researchers have also found troubling results in face mask wearers. Neurologists observed changes in MRI brain signal baseline level due to face mask use [9]. Wearing a surgical mask for merely 9 minutes increased end-tidal CO_2 causing mild hypercapnia. This was responsible for a compensatory increase in cerebral blood flow with morphological changes similar to that of a CO_2 gas challenge or holding your breath. In patients with aneurysms or brain tumours this phenomenon could be deleterious. Another study showed a pathologic and altered brain metabolism while wearing a N95 mask for 6 hours [11]. The MRI imaging revealed a significant drop in brain oxygenation. A more than 50% drop in oxygenation in the cingulate gyrus (cognition circuit) after 6 hours of mask use was associated with clinical symptoms of a confused state in 80% of the subjects above 35 years. The authors even concluded that the general population should not wear a N95 mask. This phenomenon of brain deoxygenation could be dangerous for people with altered brain functions when on medication, after a transient ischaemic attack (TIA) or stroke respectively.
Ophthalmological studies indicated risk of retinal damage from long-term use of masks. N95 masks reduced the vascular density in the vascular plexus even under resting conditions as early as after 60 minutes [138]. Here, the drop in SpO_2 and increase in blood pressure were significant but within the normal physiological range. Another study reported a significant mask-induced increase in intraocular pressure (IOP) after approx. 5 minutes of wearing [6]. Thus, wearing masks may counteract the therapy aiming to reduce the IOP and can exacerbate irreversible long-term vision problems in individuals with glaucoma. Numerous other studies have shown that the long-term effects, leading to deleterious clinical outcome may result from prolonged mask wearing [9,11,138,139]. Such effects are comparable to sick building syndrome (SBS) [140], cigarette smoking and other chronic, slightly toxic influences relevant to the general population.
In accordance with our present analysis and precedent scoping review [8], mask-related changes in leaning towards pathological values can lead to illness and clinical consequences, just like chronically, repeated subliminal harmful environmental events. Occupational diseases defined by the International Labour organization (ILO) and that are in accordance with the worker´s compensation act in Germany illustrates the potential harm caused by chronic exposure to subthreshold environmental factors [141]. Numerous examples of these principles can be found in the literature concerning pharmacology, toxicology, clinical and occupational medicine and even in

psychology [142–151]. Many other toxicological and environmental health examples are presented in the recent scoping review by Kisielinski et al [8], which refers to MIES (Mask-Induced Exhaustion Syndrome). Such subliminal chronical changes and harmful effects in the long run are comparable to the sick building syndrome (SBS) [140], cigarette smoking [152], salty diet [153], aluminium environmental pollution [154], low-level lead exposure [155], organochlorine pesticides and polychlorinated biphenyl exposure [156] or even the so-called climate change exposure [157]. Altogether, even the subliminal changes due to face mask use can become clinically relevant.

Overlapping of face mask effects (MIES) with long-COVID symptoms

Regarding the numerous mask symptoms an important question arises: Can masks be responsible for a misinterpreted long-COVID-syndrome after an effectively treated COVID-19 infection? Nearly 40% of main long-COVID symptoms [158] overlap with mask related complaints and symptoms described by Kisielinski et al as MIES [8] like fatigue, dyspnoea, confusion, anxiety, depression, tachycardia, dizziness, headache, which we also detected in the qualitative and quantitative analysis of face mask effects in our systematic review. It is possible that some symptoms attributed to long-COVID are predominantly mask-related. Further research on this phenomenon needs to be conducted.

Complaints and symptoms under mask use and the WHO definition of health

Amongst the perceived sensations with mask use only 6 symptoms (exertion, discomfort, shortness of breath, humidity, heat and itch) could be meta-analysed and have resulted in predominantly strong effect sizes (Figure 12). In the pooled prevalence analysis, we included eight main symptoms namely headache, acne, skin irritation, shortness of breath, heat, itch, voice disorder and dizziness (Figure 13) out of which all were significant in the evaluated population (Figure 8). There are many more reported in the literature. However, these could not be meta-analysed due to the low number of comparable studies on those particular complaints. In the included literature additional reported mask related symptoms were: rhinitis [80], disabilities to think and to concentrate [58,61,68,78], drowsiness [78], communication disorder [61,88,89], depression and mood swings [72,88,90,91], anger [72], perceived discomfort [41,45,52,73], anxiety [72,88,91], and an overall perceived fatigue and exhaustion [44,45,47,48,52,53,55,56,61–64,66,69,70,86].

All of these mask-related symptoms contradict a state of well-being and health as defined by the WHO. According to the WHO; “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [159]. Based on the facts we have found, the use of face mask in the hope of maintaining health is unfortunately contradicting the WHO's definition of health. Regarding all the possible side effects of mask and their still unproven efficacy against viral transmission within the general population [4,160–162], health seems not to be substantially preserved by wearing face masks. So far, only two randomized controlled mask trials for prevention of SARS-CoV-2 infection in the general population have been published: one high quality study from Denmark, Europe [163], and the other from Bangladesh with biased results and a lot of inconsistencies [164]. Based on a Bayesian random-effects meta-analysis of these two trials, the posterior median for relative risk was 0.91 (95% credible interval 0.63 to 1.33, 73% probability of some benefits with very limited evidence) [165]. The paucity in high-quality mask studies is unfortunate. Seeing the overall weak evidence for efficacy of masks against viral transmission within the general population [4,160–162,166–168], face masks have to be evaluated appropriately in the sense of the *Hippocratic Oath* and as per the *Primum nihil nocere* (above all do not harm). To avoid at all costs that the damage caused by preventive or therapeutic measures becomes greater than that caused by the disease itself, should be the credo of all those involved in the containment of the crisis, including politicians and the so-called experts. Medical decisions can only be made on the basis of comprehensive knowledge on a patient's overall condition, individualised case history, considering all previous illnesses and interventions, physical and mental predispositions and his/her socio-economic state etc. When it comes to medical decision-making in a sick person, the weighing 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 individuals, or if they are improperly applied, the consequences are usually much more severe and liability claims are often unavoidable. From a standardisation point of view the filtration efficacy of mask for viruses remains hypothetic and not in line with the established standards. There are national and international standards for bacteria filtration efficiency (BFE) for medical masks since decades, for example the EU-EN 14683, or the USA-ASTM F2101. They are the prerequisites for general approval. However, since 2020 (i.e. nearly 3 years), no comparable standard/testing of masks for viruses does yet exist. Given the fact, that medical masks (surgical and N95) increase particle exhalation in the smallest size range of 0.3 – 0.5 µm, shifting the geometric mean diameter toward smaller sizes (longer in air) compared to no mask conditions [169] doubts arise. Such scientific facts are pointing towards the nebulisation effect of masks, which could be an add-on for their weakness against viral transmission in general.

Limitations

While looking at the potential limitations our systematic review rarely discussed the inhaled toxins associated with the mask. Inhalation and ingestion of toxic substances, which are ingredients of the masks, are also of importance in evaluating this pandemic non-pharmaceutical intervention (NPI). In addition, our work has not extensively studied the microbial colonisation of masks and the consequences of contamination by microorganisms for the wearer.

Based on the studies conducted during the pandemic, the control groups without masks were mostly the same individuals, or individuals who were not mask abstinent for too long (general mask requirement)[170], so the mask-no-mask differences may be mitigated.

Because of the rapid flow of science, new interesting papers have certainly appeared that we were unable to consider in the meta-analysis as they appeared after the period of our data search (search limitation to 31.12.2021). The most important and relevant observational studies were considered for this analysis thereby addressing the physio-metabolic and clinical effects. Numerous psychological and other effects could not be assessed analytically as too few relevant and evaluable studies were available.

Conclusion

This systematic review comprehensively revealed ample evidence for multiple adverse physio-metabolic and clinical outcomes of medical face masks. This can have long-term clinical consequences, especially for vulnerable groups e.g. children, pregnant, elderly and ill. The N95 masks lead to measurably more adverse results than surgical masks. Besides transient and progressive hypoxaemia, hypercarbia and individualised clinical symptoms our findings are in line with reports on face masks driven down-stream aberrations (e.g. oxidative stress, hypercapnia, vasoconstriction, pro-inflammatory response, immunosuppression etc.) at the organ, cellular and microbiome levels and support the MIES (Mask Induced Exhaustion Syndrome). From our point of view, while a short application of the mask seems to be less harmful, longer and long-term use may cause subliminal shift of values towards the pathophysiological direction.

So far, several MIES symptoms may have been misinterpreted as long COVID symptoms.

In any case, the possible MIES triggered by masks contrasts with the WHO definition of health.

The exact threshold of harmless and non-pathogenic time wearing a mask should exclusively be determined by further intensive research and studies. Due to the ultimate lack of exclusion of the harmfulness of mask wearing, mask use by the general public should be discouraged.

From the above facts, we conclude that a mask requirement must be reconsidered in a strictly scientific way without any political interference as well as from a humanitarian and ethical point of view. There is an urgent need to balance adverse mask effects with their anticipated efficacy against viral transmission.

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Figures 1-13:

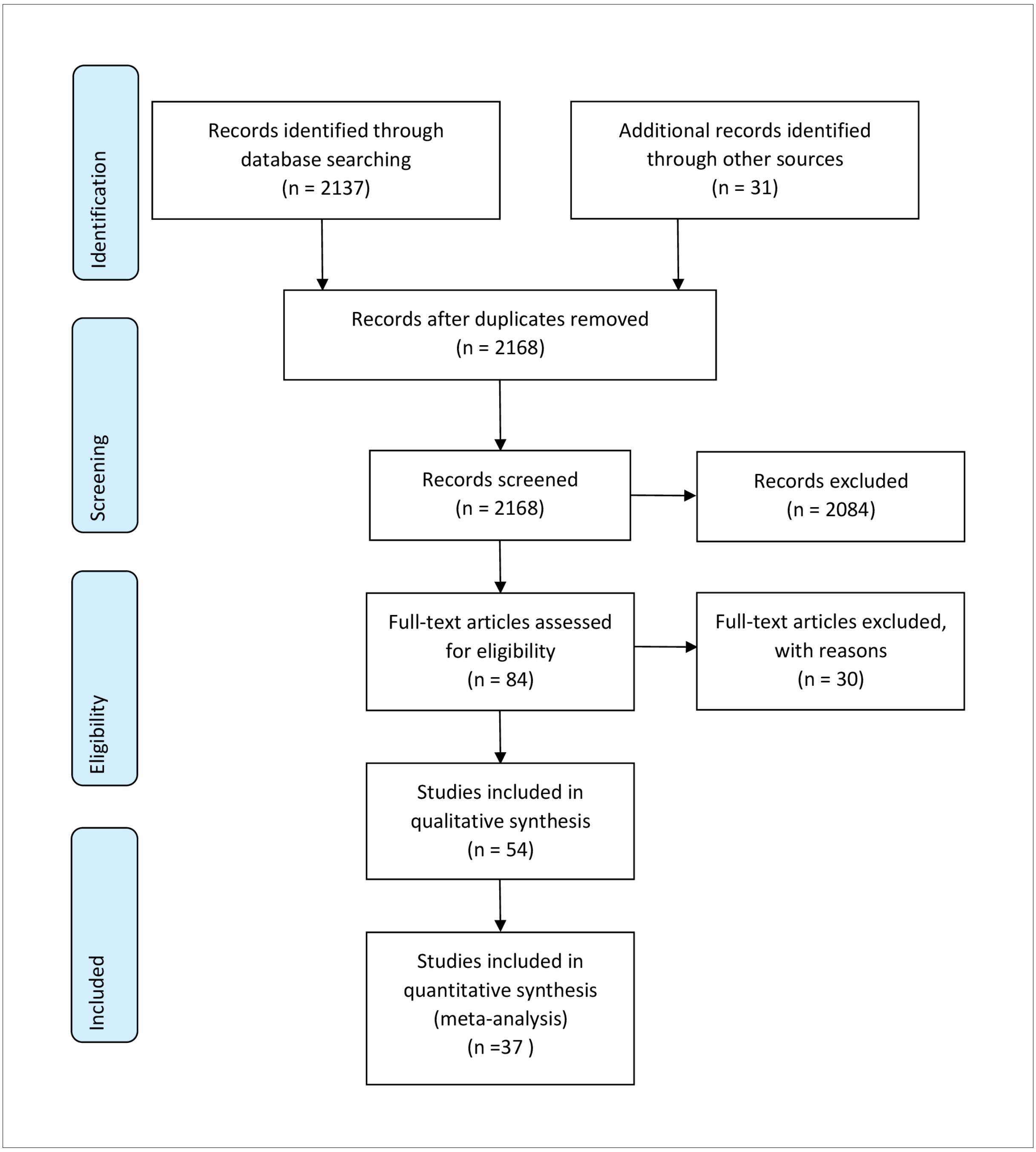

Figure 1. PRISMA flow chart of the systematic review. From initial 2168, fifty-four studies were later included in the qualitative synthesis. Finally 37 studies were evaluated statistically in the meta-analysis (quantitative analysis).

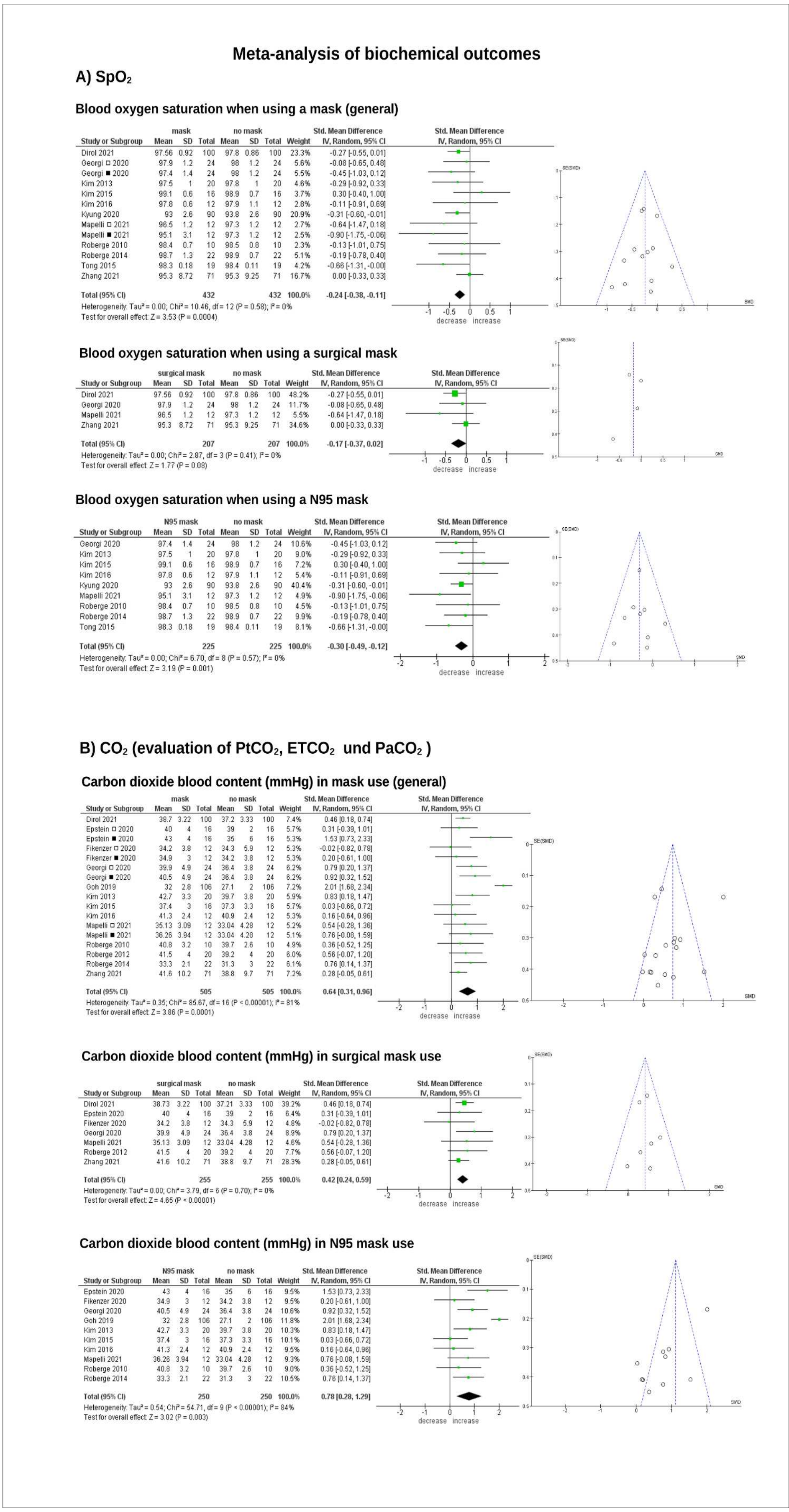

Figure 2.
Forest (left) and Funnel plots (right) of meta-analysis of blood oxygenation and blood carbon dioxide outcomes while wearing a face mask. All face mask types are initially considered together, later subgroups (surgical and N95) are evaluated. If studies examine two different mask types in parallel, the corresponding studies are marked: □=surgical mask ■=N95 mask.
A: Blood oxygen is significantly lowered in mask use. In the subgroup analysis this could also be found for N95 mask use. From the pooled analysis, it seems, that N95 mask may be responsible for a larger SpO_2 drop than surgical masks. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always lower O_2-values than the surgical masks.
B: In the pooled analysis, blood carbon dioxide ($PtCO_2$, $ETCO_2$, $PaCO_2$) is significantly elevated in mask use. This could be found for general mask use and in the subgroup analysis for surgical mask, and also for N95 mask use. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always higher CO_2-values than the surgical masks.

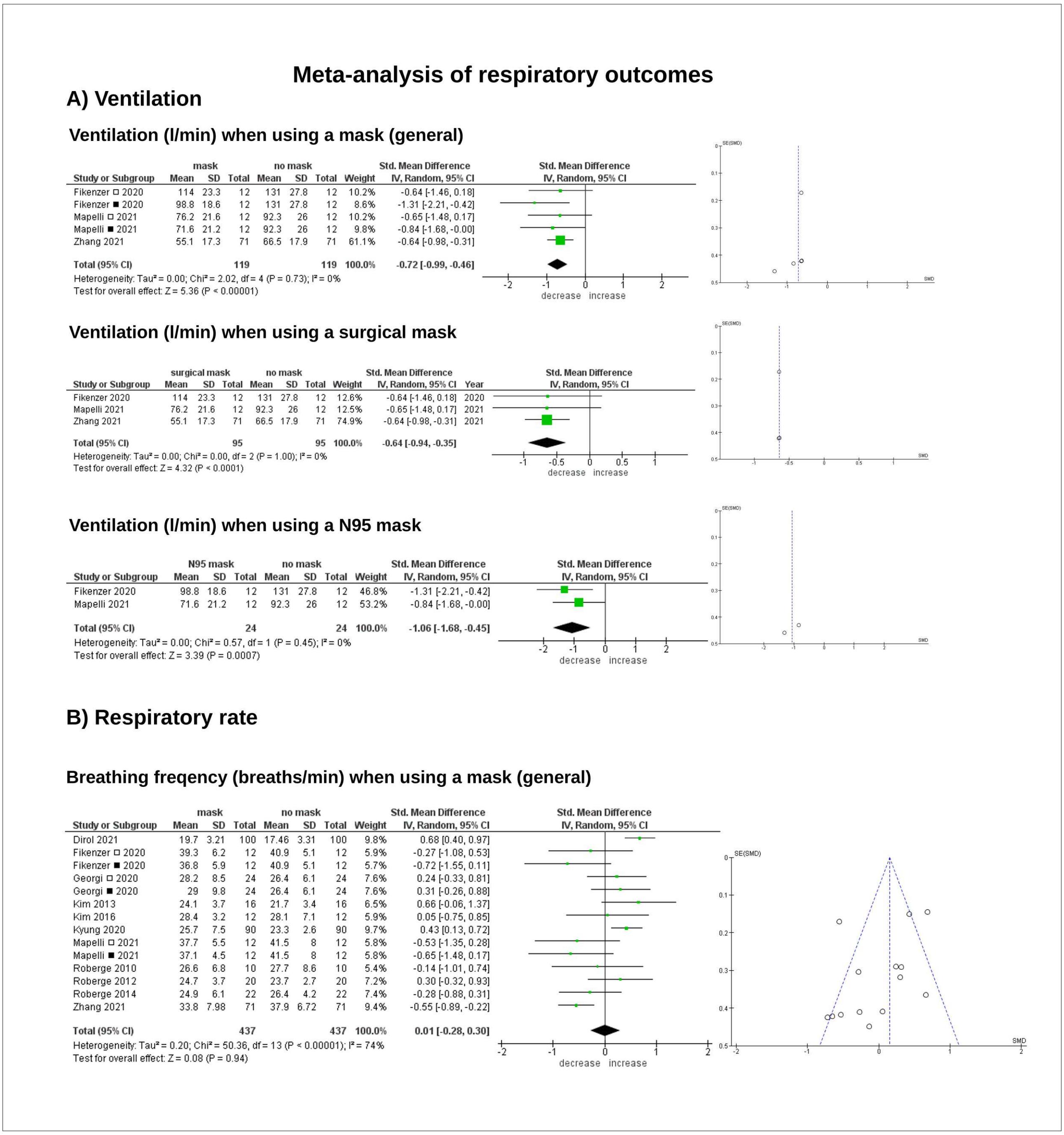

Figure 3. Forest (left) and Funnel plots (right) of meta-analysis of physiological respiratory outcomes while wearing a face mask. A shows results for ventilation (V_E), **B** for respiratory rate (RR). All face mask types are initially considered together, later subgroups (surgical and N95) are evaluated. If studies examine two different mask types in parallel, the corresponding studies are marked: □=surgical mask ■=N95 mask.

A: Breathing volume is significantly lowered in mask use in the pooled analysis. This could be found for general, for surgical, and N95 mask use. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always lower ventilation (V_E) than the surgical masks.

B: No statistical difference could be found regarding respiratory rate in mask use in the pooled analysis, even in the subgroup analysis (not shown).

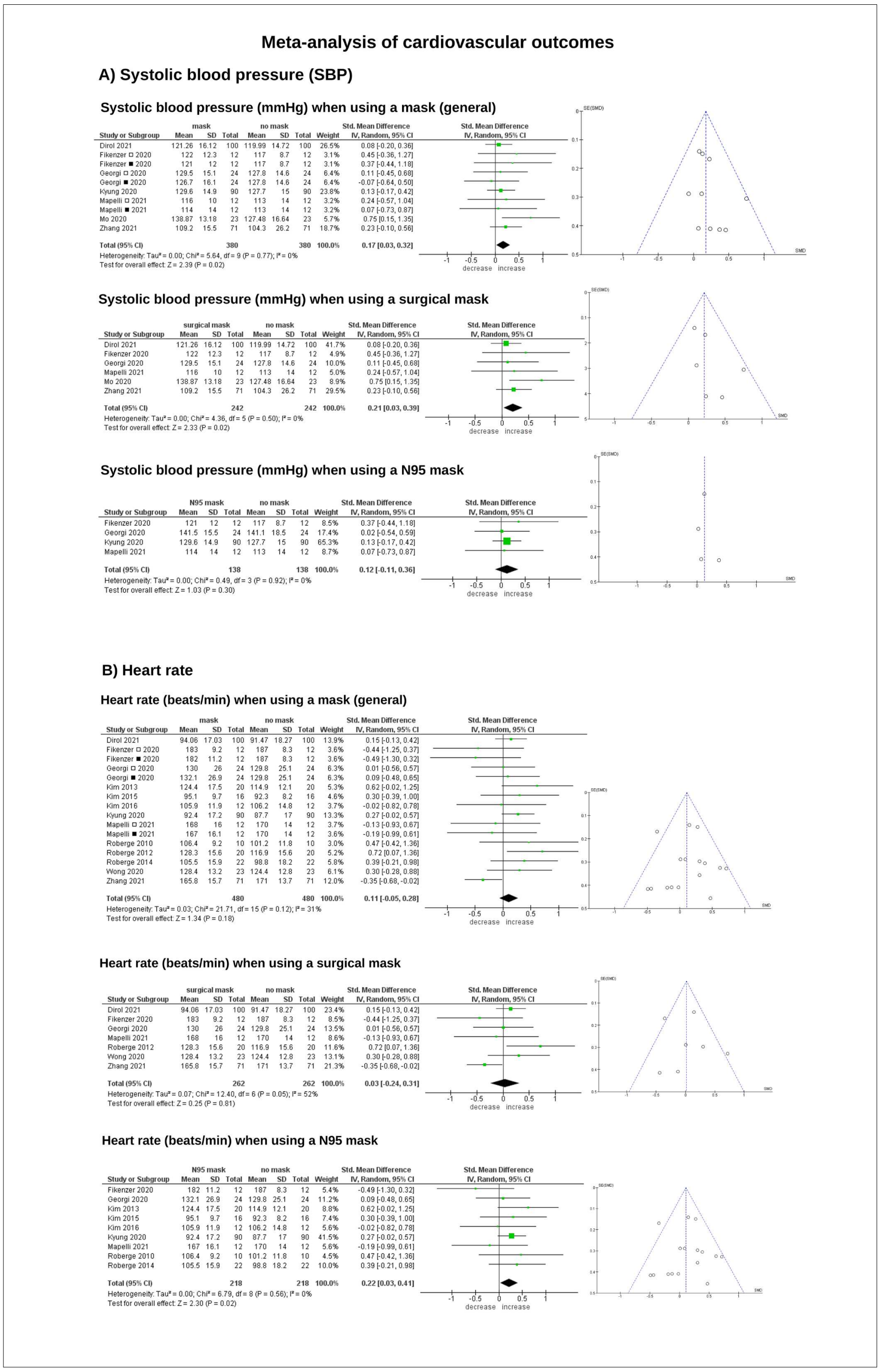

Figure 4. Forest (left) and Funnel plots (right) of metaanalysis of the physiological cardiovascular outcomes systolic blood pressure (SBP) and heart rate (HR). All controlled intervention studies in which measurements were taken during physical activity with face masks were included (exclusion of rest situation and pre-post studies). All face masks types are initially considered together, later if possible subgroups (surgical and N95) are evaluated. If studies evaluate two different mask types in parallel, the corresponding studies are marked: □=surgical mask ■=N95 mask.
A: Systolic blood pressure is elevated in the mask condition and also for the subgroup of surgical mask. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always higher SBP than the surgical mask, however this effect was not statistically significant.
B: For the N95 mask condition a low significance for a slight increase in heart rate could be found. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always higher HR than the surgical mask, and this effect was statistically significant.

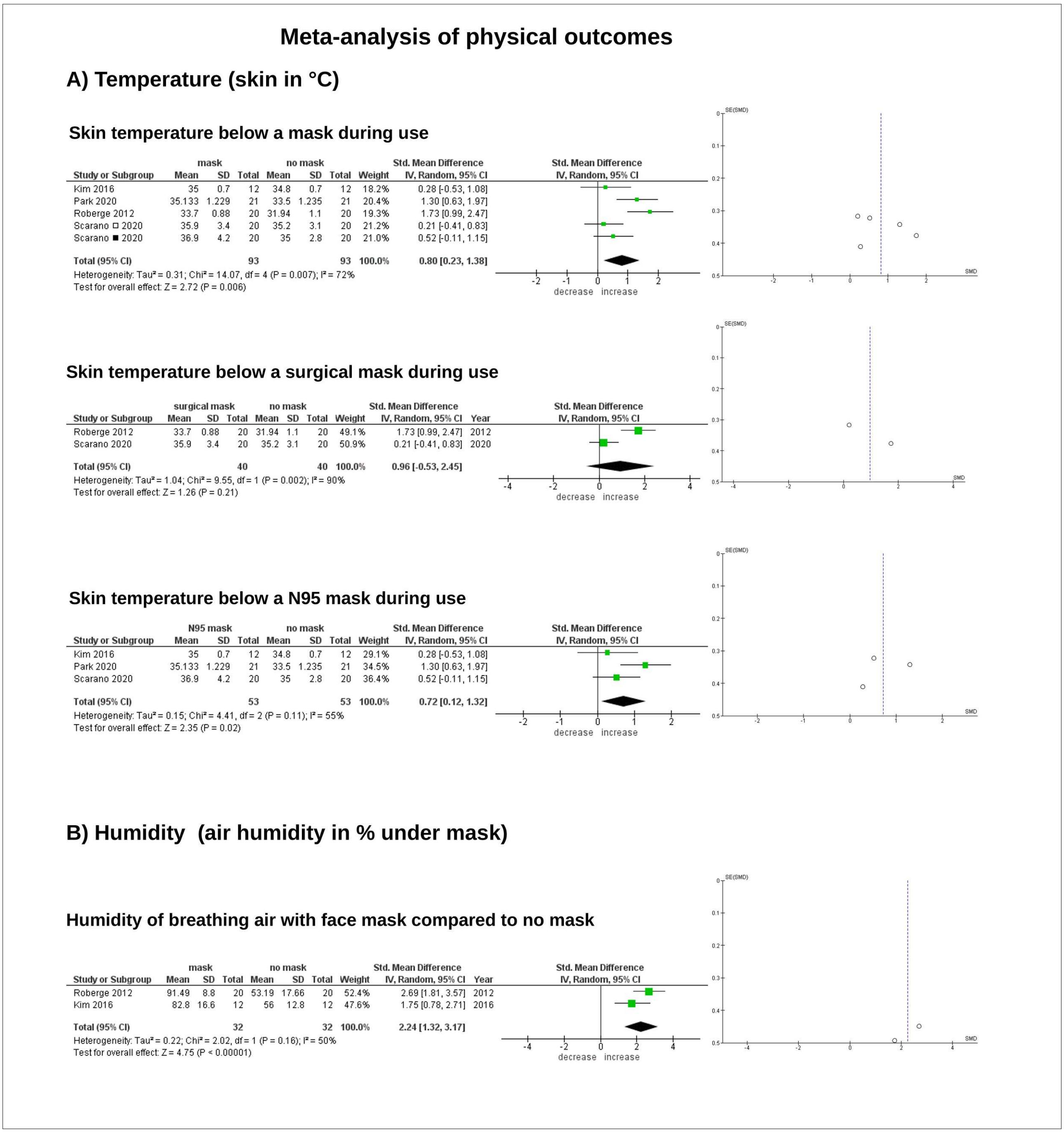

Figure 5. Forest (left) and Funnel plots (right) of meta-analysis of physical outcomes while wearing a face mask. **A** shows results for temperature of skin, **B** for air humidity underneath the face mask. All mask types are initially considered together, later subgroups (surgical and N95) are evaluated. If studies examine two different mask types in parallel, the corresponding studies are marked: □=surgical mask ■=N95 mask.

A: Skin covered by mask has a significantly higher temperature during rest and activity. This could be found for general mask use and for N95 mask use but not for surgical mask use. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded higher temperatures than the surgical mask, but this could not be analised further due to lack of further studies comparing both conditions.

B: The dead space covered by mask has a significantly higher air humidity in the pooled analysis.

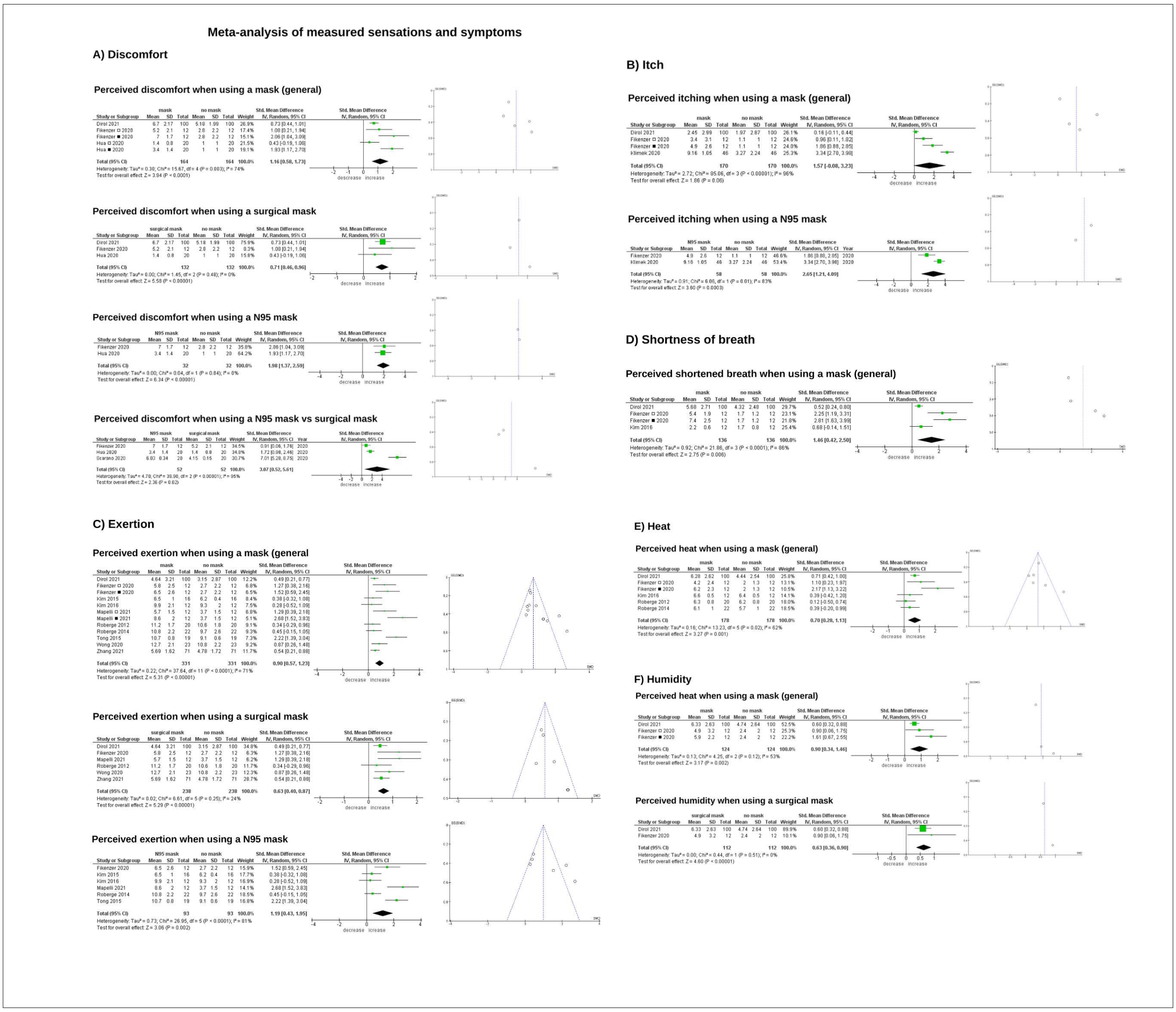

Figure 6. Forest and Funnel plots of meta-analysis of measured discomfort (**A**), itch (**B**), exertion (**C**), shortness of breath (**D**), perceived heat (**E**) and humidity (**F**) during face mask use (VAS, Likert-scales or similar). All face mask types are initially considered together, later subgroups (surgical and N95) are evaluated. If studies examine two different mask types in parallel, the corresponding studies are marked: □=surgical mask ■=N95 mask.

A: Perceived discomfort is significantly higher in face mask use in the pooled analysis. This could be found for general mask use, in the subgroup analysis for surgical-, and for N95 mask use. A pooled analysis comparing both conditions (surgical mask and N95 mask) resulted in statistically significant higher discomfort rates for the N95 mask than the surgical mask.

B: An overall significancy for itching could be found for mask use. Also in N95 mask use the perceived itching was statistically significantly elevated according to the pooled subgroup analysis.

C: In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always higher exertion rates than the surgical masks.

D: Perceived shortness of breath is significantly higher in mask use in the pooled analysis.

E: Perceived heat is significantly higher in the pooled analysis.

F: Perceived humidity is significantly higher in mask use. The subgroup analysis revealed a statistical significancy for an increase in humidity perception using a surgical mask. In studies evaluating both conditions (surgical and N95 mask) the N95 mask yielded always higher humidity perception rates than the surgical mask. A pooled analysis resulted in a statistical significance for higher humidity perception in N95 masks than surgical masks.

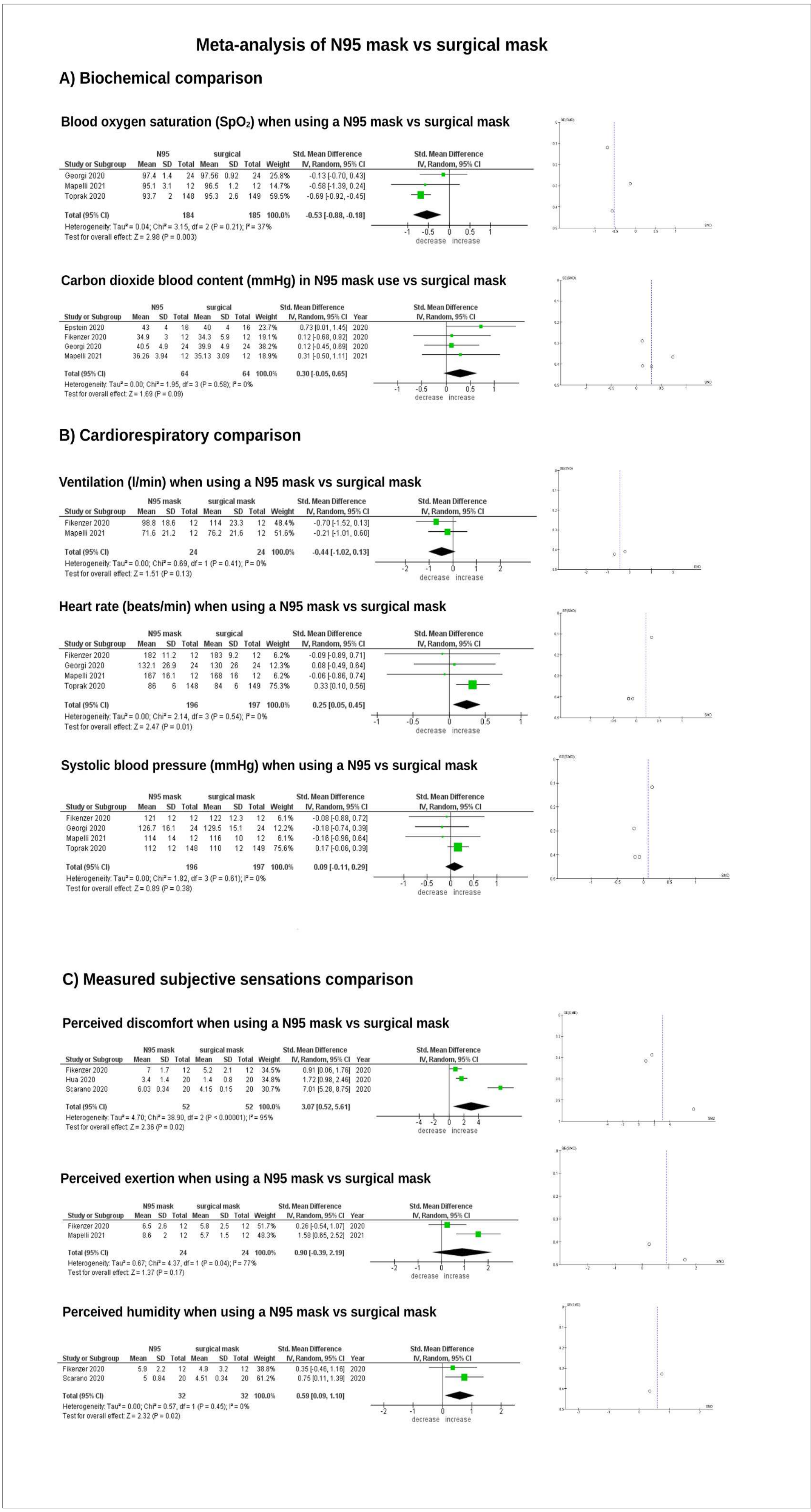

Figure 7.
Results comparing the N95 to the surgical mask in the meta-analysis. Forest (left) and Funnel plots (right) of meta-analysis of diverse outcomes while wearing a N95 mask vs surgical mask are shown. **A** depicts the biochemical, **B** the cardirespiratory outcomes and **C** the subjective sensations outcomes.
N95 mask leads to measurably less favourable results compared to the surgical mask, significantly for oxygenation (decrease), heart rate (increase), discomofort and humidity (both increases). This trend was also evident for minute volume (decrease), CO_2 and systolic blood pressure (both increases), but in those comparisons not statistically significant due to too few includable studies.

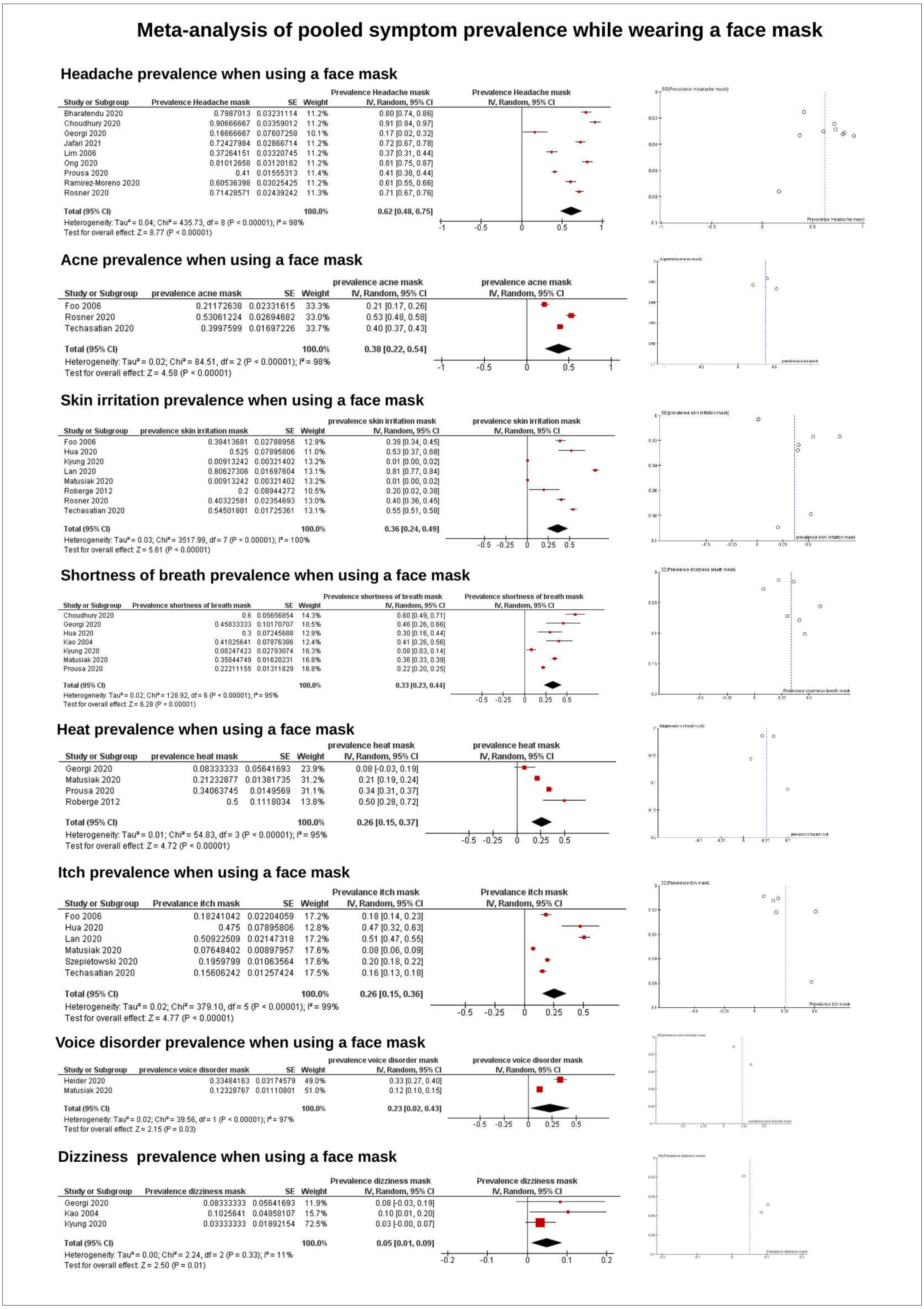

Figure 8. Forest (left) and Funnel plots (right) of meta-analysis of pooled symptom prevalence while wearing a face mask. Headache (62%), acne (38%), skin irritation (36%), shortness of breath (33%), heat (26%), itch (26%), voice disorder (23%) and dizziness (5%) while wearing a mask are significant in the evaluated population (n=8128) .

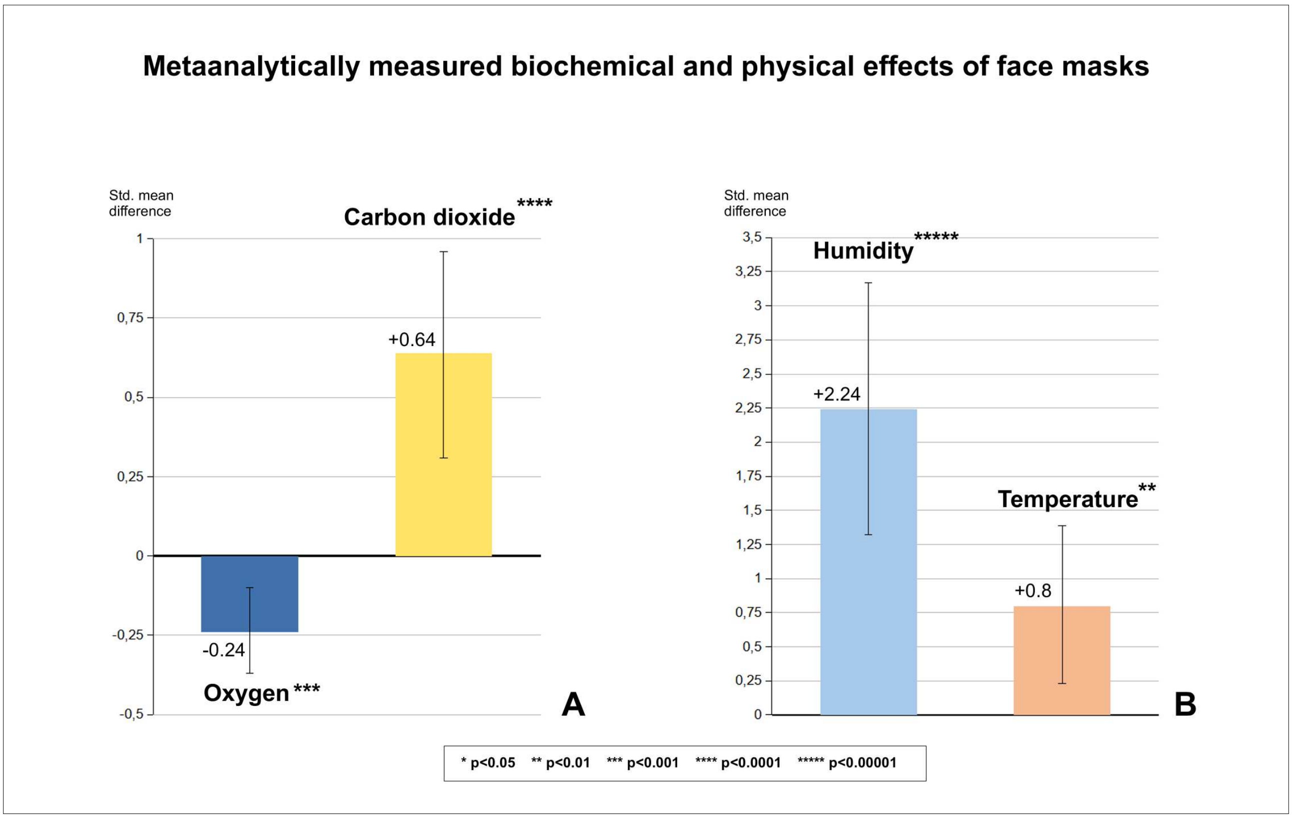

Figure 9. Summary of pooled metaanalytic evaluation of biochemical (**A**) and physical effects (**B**) during face mask use. The height of the bars reflects the SMD (standard mean difference), their error bars correspond to the confidence intervals.

A: For carbon dioxide rise in the blood there is a medium effect size of >0.5 and for oxygen drop a small effect size of >0.2 regarding the standard mean difference values thresholds according to Cohen 1988.

B: For elevated Humidity and Temperature rise under the face mask there is a strong effect size of ≥0.8.

The metaanalytical statistical data were as follows:
Oxygen (SpO_2): SMD -0.24, 95% CI -0.38 to -0.11, Z=3.53, p=0.0004;
Carbon dioxide ($PtCO_2$, $ETCO_2$,$PaCO_2$): SMD +0.64, 95% CI 0.31 to 0.96, Z=3.86, p=0.0001;
Humidity: SMD +2.24, 95% CI 1.32 to 3.17), Z=4.75, p<0.00001;
Temperature: SMD +0.8, 95% CI 0.23 to 1.38, Z=2.72, p=0.008.

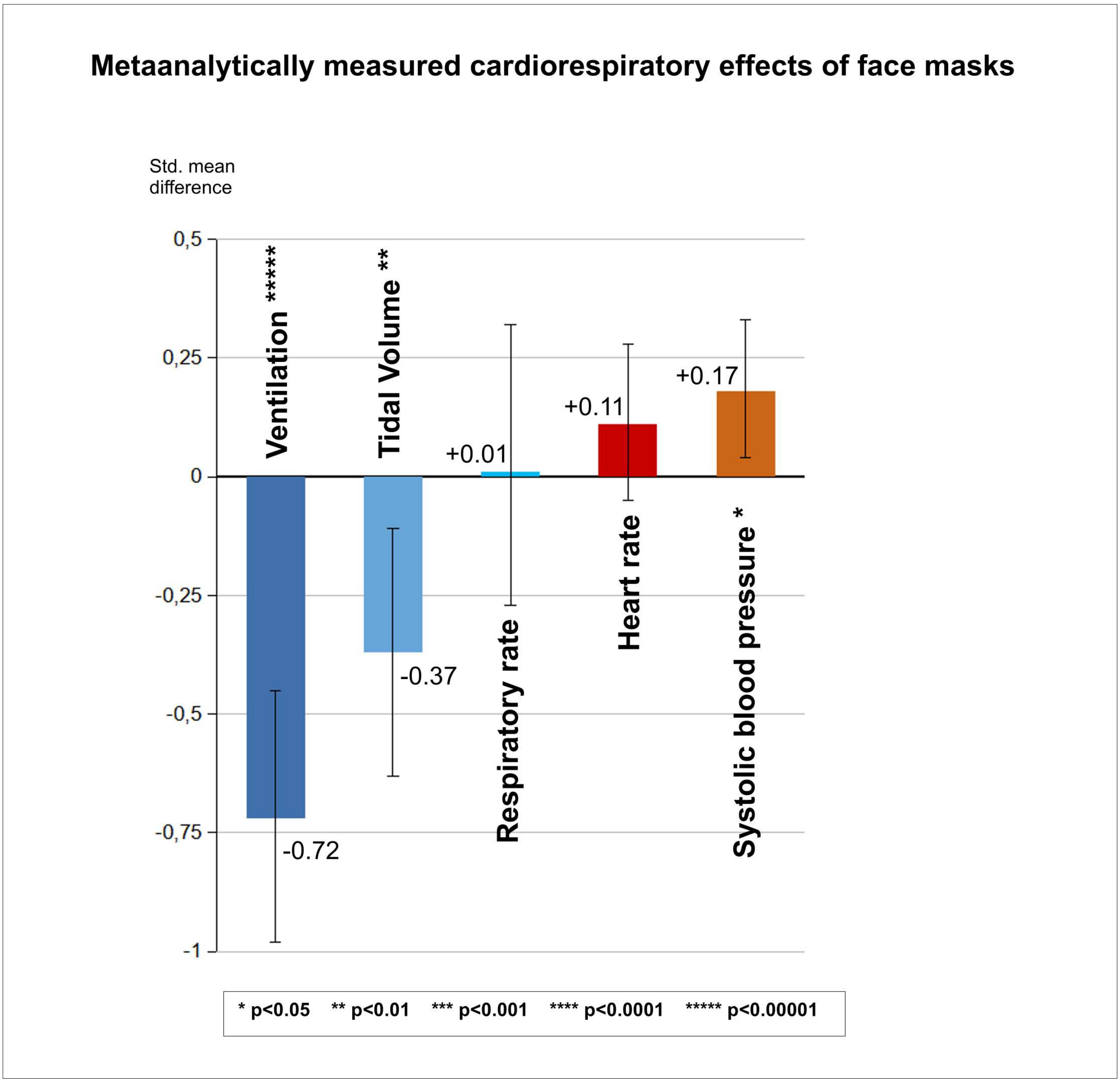

Figure 10. Summary of pooled metaanalytic evaluation of cardiorespiratory effects during face mask use. The height of the bars reflects the SMD (standard mean difference), their error bars correspond to the confidence intervals.

Clear effects for a decrease in ventilation and tidal volume are illustrated, no effect for respiratory rate and weak to low effect for increase in heart rate and systolic blood pressure. For ventilation there is a medium effect size of >0.5 with a small effect size of >0.2 for tidal volume of the standard mean difference values according to Cohen 1988.

The meatanalytical statistical data were as follows:

Ventilation: SMD -0.72, 95% CI -0.99 to -0.46, Z=5.36, p<0.00001;

Tidal volume: SMD -0.37, 95% CI -0.63 to -0.11, Z=2.82, p=0.005;

Respiratory rate: SMD +0.01, 95% CI -0.29 to 0.30, Z=0.08, p=0.94;

Heart rate: SMD +0.11, 95% CI -0.05 to 0.28, Z=1.34, p=0.18;

Sytolic blood pressure: SMD +0.17, 95% CI 0.03 to 0.32, Z=2.39, p=0.02.

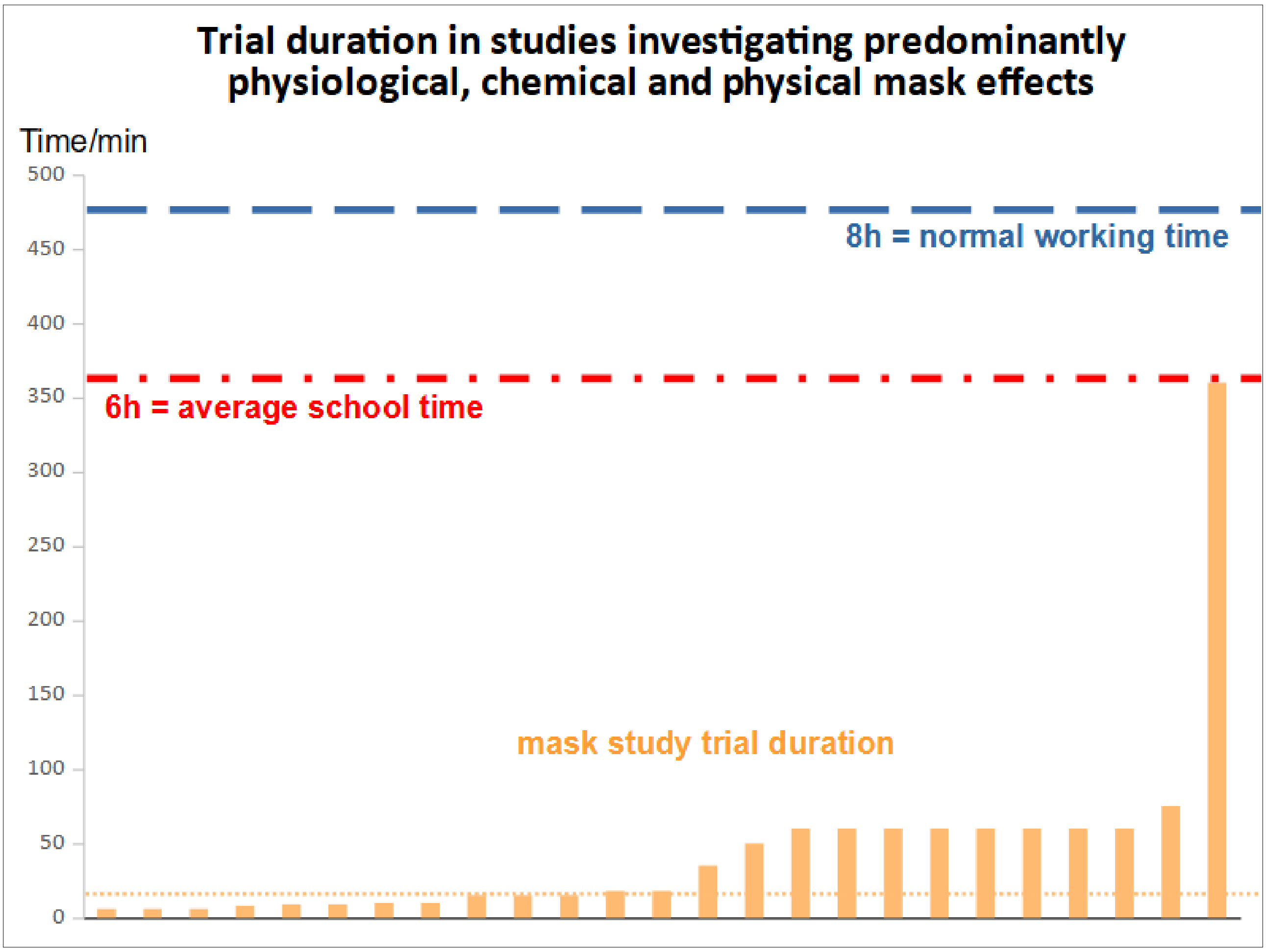

Figure 11. Illustration of the duration of studies in which measurements were made on mask effects (physical, biochemical, and physiological) in 934 participants. The median is 18 minutes (yellow dotted line) with an interquartile range of 50 . The study with the longest experimental duration included 21 subjects, corresponding to 2.2% of the total population studied. Striking not only is a very short trial time compared to the everyday scenarios workday and school attendance (see interrrupted, auxiliary lines in blue and red), but also a strongly deviating mask exposure duration with outliers (mean of 45.8 minutes with standard deviation of 69.9). Therefore, the mean is not an appropriate parameter to characterize this distribution.

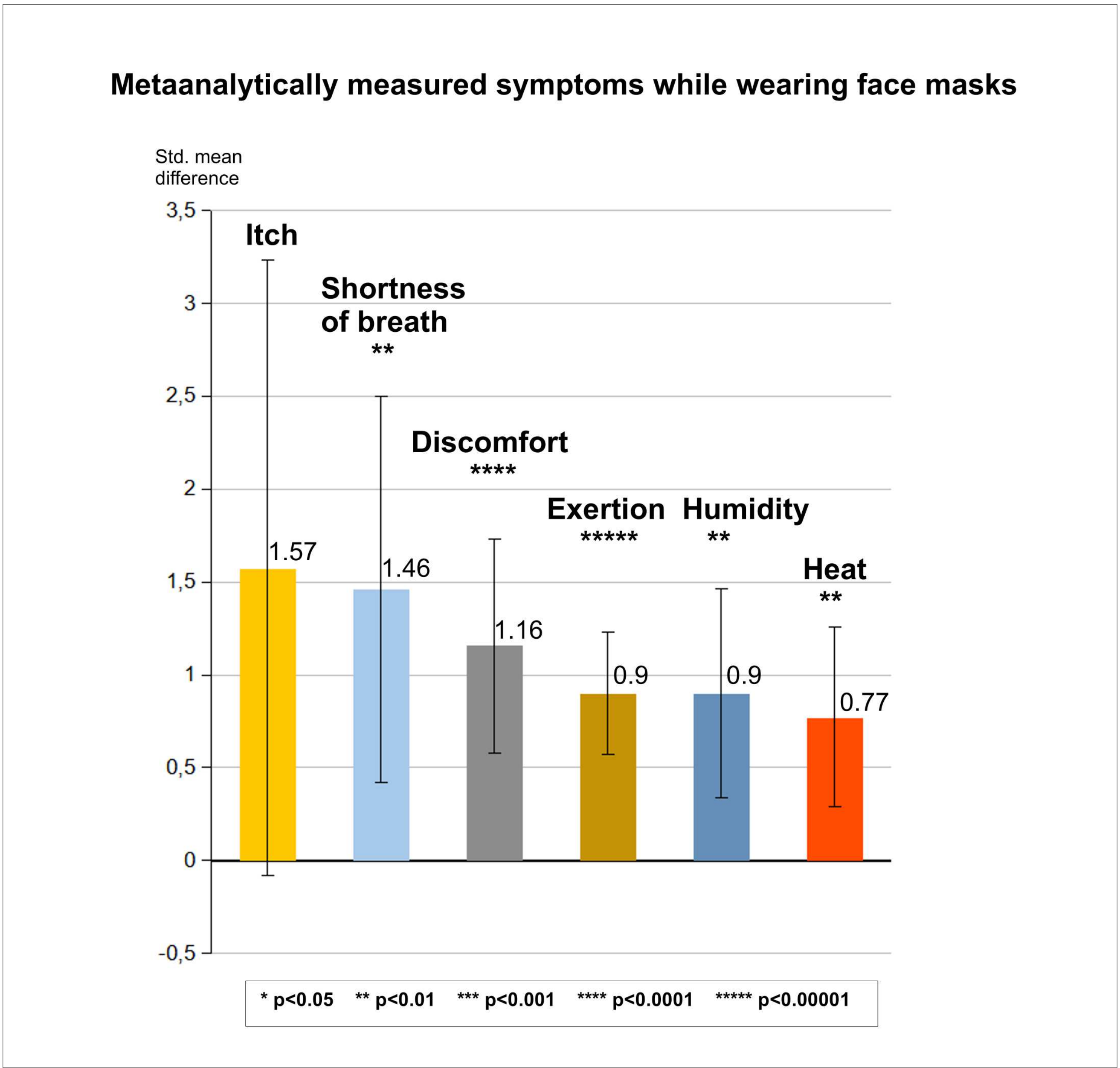

Figure 12. Summary of pooled metaanalytic evaluation of face mask-wearing sensations measured with standardised Borg-. Likert-, VAS-scales or similar. The height of the bars reflects the SMD (standard mean difference), their error bars correspond to the confidence intervals.

Five out of 6 complaint categories (83%) are above the strong effect size threshold of >0.8 of the standard mean difference values according to Cohen 1988.

The metanalytical statistical data were as follows (SMD=standard mean difference):

Itch: SMD +1.57, 95 %CI -0.08 to 3.23, Z=1.86, p=0.06;

Shortness of breath: SMD +1.46, 95% CI 0.42 to 2.50, Z=2.75, p=0.006;

Discomfort: SMD +1.16, 95% CI 0.58 to 1.73, Z=3.94, p<0.0001;

Exertion: SMD +0.9, 95 % CI 0.57 to 1.23, Z=5.31, p<0.00001;

Humidity: SMD +0.9, 95% CI 0.34 to 1.46, Z=3.17, p=0.002;

Heat: SMD +0.77, 95% CI 0.29 to 1.26, Z=3.11, p=0.002.

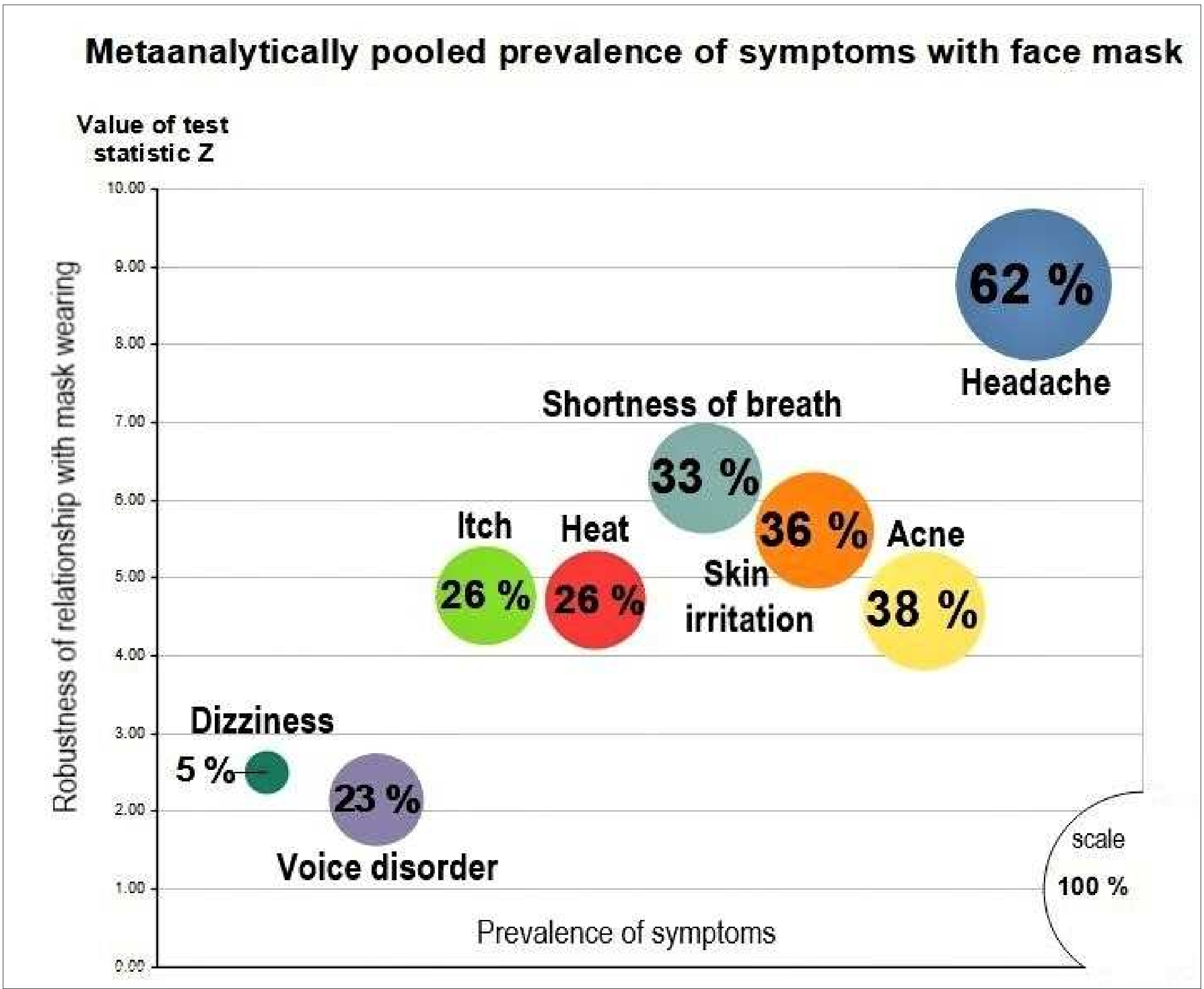

Figure 13. Representation of symptom prevalence in % during face mask use as the area of the circles. Along the X-axis, the main recorded symptoms are listed. The higher the prevalence, the bigger the circles and the more often the symptoms.

The Y-axis gives the probability of non-random occurrence of the symptoms and includes the statistical Z-value. Thus, the higher the circles are arranged, the more robust is the relationship to face mask wearing.

The meatanalytical statistical data were as follows:

Headache: 62% (95% CI 48-75%), Z=8.77, p<0.00001;
Acne: 38% (95% CI 22-54%), Z=4.58, p<0.00001:
Skin irritation: 36% (95% CI 24-49%), Z=5.61, p<0.00001;
Shortness of breath: 33% (95% CI 23-44%), Z=6.28, p<0.00001;
Heat: 28% (95% CI 15-0.37%), Z=4.72, p<0.00001;
Itch: 26% (95% CI 15-36%), Z=4.77, p<0.00001;
Voice disorder 23% (95% CI 2-43%), Z=2.15, p<0.03;
Dizziness 5% (95% CI 1-9%), Z=2.5, p=0.01.