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Review article

Impact of respiratory protective devices on respiration: Implications for panic vulnerability during the COVID-19 pandemic.

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ABSTRACT

Background: The wearing of respiratory protective devices (RPDs) correctly and continually in situations where people are at risk of respiratory infections is crucial for infection prevention. Certain people are poorly compliant with RPDs due to RPD-related annoyance, including respiratory discomfort. We hypothesized that individuals vulnerable to panic attacks are included in this group. No published studies on this topic are available. The evidence for our hypothesis was reviewed in this study as a starting point for future research.

Methods: We selected a set of experimental studies that measured the respiratory physiological burden in RPD wearers through objective and validated methods. We conducted a bibliographic search of publications in the PubMed database (January 2000–May 2020) to identify representative studies that may be of interest for panic respiratory pathophysiology.

Results: Five studies were included. Wearing RPDs exerted significant respiratory effects, including increased breathing resistance, CO_2 rebreathing due to CO_2 accumulation in the RPD cavity, and decreased inhaled O_2 concentration. We discussed the implications of these effects on the respiratory pathophysiology of panic.

Limitations: Most studies had a small sample size, with a preponderance of young participants. Different methodologies were used across the studies. Furthermore, differences in physical responses between wearing RPDs in experimental settings or daily life cannot be excluded.

Conclusions: This research supports the idea that panic-prone individuals may be at higher risk of respiratory discomfort when wearing RPDs, thereby reducing their tolerance for these devices. Strategies to decrease discomfort should be identified to overcome the risk of poor compliance.

1. Main body

Outbreaks of emerging infectious diseases over the recent years, including the ongoing coronavirus disease 2019 (COVID-19) pandemic, have led to the recommended routine use of respiratory protective devices (RPDs) for healthcare workers (HCWs) to reduce the risk of exposure. Furthermore, the most recent recommendations of the World Health Organization and the US Centers for Disease Control and Prevention (CDC) include the wearing of face masks by the general public among the strategies for mitigating the risk and impact of COVID-19 (CDC, 2020). The most used RPDs among HCWs and the general population are surgical facemasks (SMs) and filtering facepiece respirators (FFRs), which include N95 (American standard, CDC), FFP2 (i.e., the closest European equivalent to N95), and FFP3 masks (Baig et al., 2010; Wizner et al., 2018).

The correct and continual wearing of RPDs is crucial in situations where people are at risk of respiratory infections. To date, the use of RPDs is mandatory among HCWs in Italy, as per the guidelines for HCWs of the Lombardy Region (Regione Lombardia, 2020a), while it is mandatory or highly recommended, depending on the context, among the general population, as per Regional Ordinance No 314 of 03/21/2020 and subsequent inclusions and modifications of the Lombardy Region guidelines (Regione Lombardia, 2020b). As psychiatrists and psychologists who are experts in anxiety disorders and work in Northern Italy, one of the areas most affected by the COVID-19 pandemic, we have observed significant difficulties in our patients when wearing RPDs because of physical symptoms and discomfort. In our current clinical experience, patients suffering from panic attacks (PAs) or panic disorder (PD) are the most afflicted by physical symptoms, mainly respiratory, related to the use of RPDs. During psychiatric visits

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Table 1
Details of the selected studies

Study	Main aim	Sample	Procedure	Main physiological measures	Instruments	Main results of interest	Other results of interest	Main limitations/ Comments of interest
HUMAN STUDIES								
Lee and Wang, 2011	To asses objectively the impact of wearing N95 respirators (without EV) **on breathing resistance**.	N = 14 healthy volunteers (7 M, 7 F; aged from 18 to 25 years). No medication intake; no respiratory symptoms/ diseases, assessed by rhinological examination	One week prior the experiment: Respirator fit test for each participant. Experiment: Participants underwent rhinomanometry and rhinospirometry (after being relaxed for 30 minutes) when wearing an N95 respirator and when not wearing it. During the measurements, they were asked to breathe in a relaxed manner through the nose.	**Nasal airflow resistance** [measured as a total pressure/flow (Pascal seconds per cubic meter)] and air exchange (i.e., the volume of air inspired and expired through the nose). All measures were recorded by a mean of at least 3 consecutive tests with stable results. Measures with versus without N95 respirator were compared	Rhinomanometer NR6-2 and Rhinospirometer NV1 (GM Instruments, UK), with a modified full-face mask to provide proper fitting when wearing N95 respirator.	With the use of N95 respirators: **a mean increment of 126.4%** (range: 7.9%-327.6%) (SD, 99.3%) **and 122.6%** (4.3%-367.7%) (SD, 103.3%) **in inspiratory and expiratory flow resistances**, respectively, and **a mean reduction of 37.4% in air exchange** (range: 5.1%-91.3%) (SD, 29.7%)		Main limitation: Very small sample size. To note: the range of values of the respiratory measures in the sample was very wide, suggesting a pronounced subjective variability in respiratory responses when wearing N95 respirators.
Laferty and McKay, 2006	To asses and **compare physiologic effects** during QLFT* and QNFT with two types of respirators (i.e., **Full-FR**, equipped with high efficiency filters, **and N95 FFR without EV**)	N = 20 healthy volunteers (10 M, 10 F); mean age, 30 years (SD, 6.2). All participants passed medical clearance.	User seal checks before performing fit tests. Multiple fit tests were conducted (with at least 2 minutes without respirator between each test) using the standard set of exercises recommended by OSHA**	CO2 and O2 levels (%) inside respirators (measured 30 seconds after the end of each test); heart rate and arterial O2 saturation (measured before and after each test).	GEM-500 infrared gas analyzer connected to a port in respirators; N200 Pulse Oximeter and DS-100A Durasensor.	During QNFT: **Mean CO2 levels = 2.8%** (SD, 0.5%) with **N95 FFR**, and **2.1%** (SD, 0.4%) **with Full-FR; mean O2 levels = 17.1%** (SD, 0.5%) with **N95 FFR**, and **18.3%** (SD, 0.5%) with **Full-FR**.	During QLFT, CO2 level further increased, and O2 levels decreased, than during QNFT (Mean value CO2: 4.2%, SD, 0.4% with N95 FFR; 3.2%, SD, 0.4% with Full-FR. Mean value O2: 15.5%, SD, 0.6% with N95 FFR; 16.7%, SD, 0.6% with Full-FR). In both QLFT and QNFT heart rate, O2 saturation, and breathing exertion (Borg Ratio Scale) did not significantly differ than pre-test condition.	Main limitation: Small sample size. To note: during both the QNFT and QLFT, **the CO2 levels in in respirators' microenvironment exceeded the recommended threshold, while the O2 levels were considered as O2 deficient**, according to different guidelines concerning workplace atmosphere ***
Roberge et al., 2010	To assess **physiological effects of wearing N95 FFR**, with and without an EV, in HCWs.	N = 10 healthy volunteers, HCWs (3 M, 7 F, aged from 20 to 45 years) who were experienced with wearing FFRs. All participants passed medical clearance.	Before the experiment: quantitative respirator fit test with the device TSI PortaCount Plus, TSI (all participants: overall fit factor ≥100). Experiment: Each participant underwent multiple 1-hour (i.e., mean nurse FFR wear time per shift) treadmill walking sessions (2 sessions per day, with a minimum 30-min break between sessions), at 1.7 miles/h (2.74 Km/h), and 2.5 miles/h (4.02 Km/h), while wearing N95 FFR with EV, N95 without EV, and without	**CO2 and O2 levels** in the N95 FFR's dead space, heart rate, respiratory rate, tidal volume, minute ventilation, O2 saturation and CO2 partial pressure (transcutaneous measurements).	LifeShirt System with physiological sensors and respiratory-inductive-plethysmography bands. O2 and CO2 gas analyzer connected to a port in the N95 FFRs. Tosca 500 monitor for transcutaneous measurements: Pulse oximeter and Severinghaus-type heated sensor (potentiometric measures)	The time-averaged **CO2 and O2 levels** in N95 FFR's dead space, over 1 hour, were, respectively, **2.9% (SD, 0.4%) and 16.6% (SD, 0.5%)** for **N95 without-EV,** and **2.9% (SD, 0.5%) and 16.7% (SD, 0.9%)** for **N95 with-EV** (No significant differences between the two respirators at both work rate). No significant differences were found in the other physiological parameters between control condition and	Two participants reported higher than normal transcutaneousCO2 partial pressure (peak 60-minutes = 50 and 52 mm Hg), suggesting the potential for substantial CO2 retention with both types of respirators. No significant differences in exertion (Borg Perceived Exertion Scale) between the different conditions were found.	Main limitation: Very small sample size. To note: As in the above-described article, the **CO2 and O2 levels in respirators' microenvironment did not meet the recommended standards for workplace atmosphere*****. The impact on other respiratory variables were modest and non-significant, indicating a mild added effort required to overcome the filter-media resistance.

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Table 1 (*continued*)

Study	Main aim	Sample	Procedure	Main physiological measures	Instruments	Main results of interest	Other results of interest	Main limitations/ Comments of interest
			N95 FFR (control session). Respirators were assigned in a random order; treadmill speeds (very low workloads) were considered representative of usual HCWs' activity levels			the two respirators, except for higher respiratory rate with N95 with-EV than with N95 without-EV.		
Smith et al., 2013	To evaluate if **speech and exercise workload** influence **CO2 levels** when wearing a **SEA Full Face Mask-SMF-L**, with side-mounted filter on one side.	N = 40 healthy volunteers (39 M, 1 F, aged from 19 to 58 years, median: 34 years) who worked at a refinery and were familiar with the use of RPDs. Non-smokers = 32; physically active/exercise on regular basis = 22. All participants passed medical clearance, did not suffer from claustrophobia and did not obtained State or Trait Anxiety Scale Scores at the 90th percentile or above.	Before the experiment: quantitative respirator fit test with the device TSI PortaCount Plus, TSI (inclusion criterion: overall fit factor > 500). Experiment: graded exercise test on a cycle ergometer that increased in workload every 5 minutes; during the third minute of each stage, participants read aloud a prepared text.	**PICO2**, PECO2, heart rate, respiratory frequency, peak inspiratory air flow, VO2. Variables were calculated across 6 workloads (rest, 75/ 100/125/150/175 W) and two breathing conditions: speech and no speech.	Validyne P55D Pressure Transducer (pressure probe); two gas sampling lines to collect inspired and expired gas samples within the oronasal cup; O2 and CO2 gas analyzer. Stationary cycle ergometer; Polar heart rate monitor.	**Mean PICO2** in **no speech-condition** ranged from **1.5%** (SE, 0.06%) (at rest) **to 1.0%** (SE, 0.04%) (at 175 W), while in **speech-condition** it ranged from **2.1%** (SE, 0.08%) (at rest) **to 1.4%** (SE, 0.03%) (at 175 W). Mean PICO2 in speech-condition was significantly higher than in no-speech condition across all the workloads except for 175W. At rest (speech), 3 participants experienced > **3%** PICO2; during periods of work (speech), 11 participants experienced > **2%** PICO2.	On average, PECO2 was higher during periods without speech. The highest mean PECO2 was 5.8% (at 75 W-speech, and at 100 W-no speech); the lowest mean PECO2 was 2.8% (at rest-speech). On average, breathing frequency (BF) was reduced during speech. At rest, during speech, BF decreased by 23.5%. **Dyspnea** (Modified Borg Scale) rose during both increases in exercise effort and periods of speech.	Main limitation: Under-representation of women. To note: **Periods of speech** (many occupations require workers to communicate while wearing RPDs) **increased inspired CO2 well above the normal concentration in atmospheric air (i.e., 0.03%) and above the AS/ NZs, OSHA, and European standards for the respirator design****
BREATHING SIMULATION STUDY								
Zhang et al., 2016	To investigate the **flow-field in the upper respiratory system, using a reverse modeling of a headform when wearing a N95 FFR and a CFD simulation** based on the modeling.	-	A headform wearing a N95 FFR was built based on a Computed Tomography scanning using a reverse modeling approach. Reverse modeling is an approach of the Computer-Aided Design (CAD) model reconstructed from a physical object	**CO2 volume fraction**, temperature, and pressure **inside the N95 FFR cavity** (dead space) during simulation of full breathing cycles.	The CDF simulation of full breathing cycles was implemented using CFD software (FLUENT12.0, ANSYS, Canonsburg, PA). The numerical model contained all the relevant components: human upper airways, FFR cavity (dead space), FFR media, and ambient air	Wearing an N95 FFR resulted in **CO2 accumulation** (CO2 volume fraction was **1.2% after 7 breathing cycles** and **then** was **maintained at 3.04% on average**), **increase in temperature** [rapid increase followed by a plateau (32-33°C at 8 minutes)], and **pressure elevation** (the percentage increments in expiratory and inspiratory resistance	-	Main limitations of the model: the removal of the metal nasal bar; the respiration cycle was constant (while the body changes the respiration cycle to compensate); the recumbent position of the subject in CT scanning to build the headform. To note: **The wearers re-inhale excessive CO2 in every breathing cycle from the N95 FFR cavity.**

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Table 1 (*continued*)

Study	Main aim	Sample	Procedure	Main physiological measures	Instruments	Main results of interest	Other results of interest	Main limitations/ Comments of interest
						were 283.5% and 299.8%, respectively; approximately 90 Pa more pressure was needed to keep the same expiratory flow rate of 30.54 L/ minute, compared with condition of no wearing the FFR), **in the N95 FFR cavity**		

CO2 = carbon dioxide; CDF = computational fluid dynamic; EV = exhalation valve; Full-FR = Full Facepiece Respirator; HCWs = healthcare workers; N95 FFR = N95 filtering facepiece respirator;; M = males; OSHA = Occupational Safety and Health Administration; O2 = oxygen; PICO2 = Percentage of mixed inspired CO2; PECO2 = Percentage of mixed expired CO2; QLFT = respirator qualitative fit test; QNFT = respirator quantitative fit test; RPDs = respiratory protective devices; SD = standard deviation; SE = standard error of the mean; VO2 = rate of oxygen uptake.

* During QLFT, a test hood is positioned over a person's head and shoulders while he/she wears a respirator.

** Standard set of exercises recommended by Occupational Safety and Health Administration (OSHA) for fit testing: normal breathing, deep breathing, turning head side to side, moving head up and down, talking, bending over (or jogging), and grimace (smile or frown) (one minute each).

*** The recommended OSHA Permissible Exposure Limit (PEL) and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value is 0.5% CO2 in workplace atmosphere [averaged over an 8-hour workday (time-weighted average or TWA)] to minimize the potential for asphyxiation and undue metabolic stress. A ceiling exposure limit (not to be exceeded) of 3% CO2 in short term (10 minutes) exposure periods (STEL, short term exposure limit) is recommended by the ACGIH. The ACGIH and the National Institute of Safety and Health (NIOSH) consider a 30-minute exposure to 4% CO2 in ambient atmosphere as dangerous for health. The OSHA definition of O2 deficiency is an atmosphere that contains less than 19.5% O2 by volume (OSHA – Carbon dioxide report - https://www.osha.gov/chemicaldata/chemResult.html?RecNo=183).

**** The Australian/New Zealand (Standards Australia - AS/NZS - SF-010 Occupational Respiratory Protection 2015 - "Respiratory Protective Devices" - https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.134), OSHA (1910.134 - "Respiratory Protection" - https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.134), and European (EN 13274-6 last release 2019 – "Respiratory protective device") standards specify that CO2 should not exceed 1% for more than one consecutive minute when testing RPDs.

at our facilities, they often complain about these symptoms and ask for permission to move or remove their RPDs, and they report similar symptoms that lead urgency in moving or removing the devices in their daily life. Unfortunately, being poorly compliant in RPD use may increase their risk of contracting COVID-19 (CDC, 2020). Moreover, many patients worry that their discomfort could become evident to others who may judge them for moving their RPDs or even for their urgency in removing the devices while in social contexts where removal is not recommended. This concern may worsen social avoidance and agoraphobia, two conditions often associated with PD.

In line with our experience, some studies revealed that certain people in the general population appeared to repeatedly move their masks, touch them, or not to wear them when required due to multiple physiological and psychological sources of RPD-related discomfort, thereby decreasing infection prevention. For the same reasons, even HCWs, a category of people who are supposed to be well trained on this issue, were often found to be poorly compliant with RPDs (Baig et al., 2010; Johnson, 2016; Wizner et al., 2018). Respiratory discomfort is a main complaint of RPD wearers, and it was found that approximately 30% of HCWs complained of breathing difficulties most of the time or always when wearing an N95 respirator. A further 34% of HCWs declared difficulty breathing some of the time, while 36% never or rarely complained of breathing difficulties (Baig et al., 2010). In line with this, increased levels of anxiety related to a sense of claustrophobia have been described by the wearers of different RPD types (Baig et al., 2010; Johnson, 2016).

Although limited, these findings suggest that the degree of respiratory discomfort varies considerably among wearers. Since wearing RPDs may induce a real burden of respiratory effects, it is conceivable that the levels of subjective respiratory and emotional responses arise from the interplay between the physiological effects of RPDs and the individual's sensitivity to them. Driven by our current clinical observations and based on the well-established panic–respiration connection, we hypothesized that individuals with vulnerability to PAs, with or without full-blown PD, can be included among RPD wearers at risk of high respiratory discomfort. Experimental evidence has supported the hypothesis, unique in the realm of mental disorders, that subclinical alterations of basic physical functioning, mainly of the respiratory system, may be involved in the pathogenesis of PAs (Caldirola and Perna, 2019). Although the source of these features remains unclear and required further discussion, patients with PD, from a clinical point of view, experience a significant burden of respiratory and physical symptoms or discomfort during PAs, as well as in several environmental situations. Furthermore, the fear of suffocation is one of their primary fears, and they usually develop attentional bias toward somatic sensations, proneness to catastrophic misinterpretation of normal bodily changes, and interoceptive/exteroceptive conditioned responses. Finally, some authors proposed that the fear and concerns about somatic sensations may be even more pronounced in those patients with PD patients who present alexithymia (De Berardis et al., 2013, 2007). Overall, patients with PD seem to exhibit greater physical and emotional difficulties in coping with somatic sensations and internal bodily changes compared with individuals suffering from other anxiety disorders (Hoehn-Saric et al., 2004; Rudaz et al., 2010).

To date, there is a lack of studies evaluating the subjective or objective impact of wearing RPDs in individuals with PAs or PD. This brief narrative review provides an empirical starting point for future research on this topic. It summarizes the main respiratory effects of common RPDs and discusses their implications on the pathophysiology of individuals vulnerable to panic. We conducted a bibliographic search of the PubMed database for articles published between January 2000 and May 2020 that aimed to measure the respiratory physiological burden in RPD wearers. We used the following keywords in combination: *respirator(s), face mask(s), respiration, breathing, resistance, ventilation, CO_2, carbon dioxide, O_2,* and *oxygen.* We aimed to select representative studies that may be of interest for panic respiratory pathophysiology. We selected four representative studies that satisfied the inclusion criteria of providing objective measurements of respiratory parameters measured using validated methods of recordings and calculations in healthy individuals (i.e., without medical diseases) aged ≥18 years when wearing RPDs. We also included one study performed using a computational breathing simulation, as representative of the body of research that investigated the impact of RPDs on physiological functions using computerized devices and techniques without human subjects (Table 1).

1.1. Impact of RPDs on respiration

The four selected studies that collected objective measures in healthy individuals wearing RPDs (N95 FFRs or full facepiece respirators) revealed some significant respiratory effects, both in those who were experienced with wearing these devices (Laferty and McKay, 2006; Lee and Wang, 2011) and those who were not (Roberge et al., 2010; Smith et al., 2013), and this was also found by (Zhang et al., 2016) using a computational fluid dynamics simulation of full breathing cycles. Table 1 reports a detailed description of the studies, including the sample characteristics, procedures, and main results of interest. Overall, RPDs may alter the users' natural breathing patterns and make breathing more difficult.

Firstly, an increase in breathing resistance was found, with percentage increments in expiratory and inspiratory flow resistance reaching up to approximately 300% (Lee and Wang, 2011; Zhang et al., 2016). This increment may induce a significant increase in respiratory effort to overcome resistance and maintain adequate expiratory flow rates (Lee and Wang, 2011; Zhang et al., 2016). It may also lead to hypoventilation, as suggested by the average decrease of 37% in air exchange volume found in N95 FFR wearers by (Lee and Wang, 2011). The increased breathing resistance, in association with CO_2 rebreathing while wearing RPDs (see below), may amplify respiratory fatigue and impair physical work capacity (Smith et al., 2013). However, although most results pointed to an increase in breathing resistance while wearing RPDs, the range of resistance-related respiratory values varied widely both across studies and across participants in the same study. Furthermore, (Roberge et al., 2010) did not observe indications of increased respiratory effort in RPD wearers when assessed at very low workload for a relatively brief period of time. This variability suggests that a pronounced subjective diversity in respiratory sensitivity may exist in individuals wearing RPDs and that certain conditions (e.g., higher workloads, during speech, or prolonged periods of RDP use) may exert a greater impact on respiration than others.

Secondly, facepiece dead volume (i.e., the void between the respirator and the face) accumulates exhaled CO_2, which is inhaled during the next inspiration. Hence, the dead volume, in association with hypoventilation related to increased breathing resistance, can contribute to CO_2 rebreathing while wearing FFRs., Dead space CO_2 accumulation in individuals wearing RPDs during common conditions, such as at rest, during speech or at low work rates, ranged from ≥1.5% to approximately 3% in the reviewed studies. This is up to 100 times higher than that expected in normal environmental air (0.03%–0.04%) and well beyond the recommended CO_2 thresholds in the workplace environment (i.e., 0.5%, averaged over an 8-h work day) or in respirators' microenvironment when testing RPDs (i.e., CO_2 should not exceed 1% for more than 1 consecutive minute), as indicated by the guidelines of several regulatory organizations (details in Table 1). It is well known that a prolonged exposure to 2%–3% CO_2 may generate headache, sweating, dizziness, and dyspnea, even in individuals without medical diseases (Johnson, 2016).

Finally, the increased RPD-related dead space was found to lower the average inhaled O_2 concentration. (Laferty and McKay, 2006) and (Roberge et al., 2010)found O_2 levels inside respirators' cavities ranging from 16.6% to 18.3%, which represent an O_2-deficient space, according to the recommended threshold of the Occupational Health and Safety

Administration (O_2 deficiency is an atmosphere that contains <19.5% O_2 by volume) (Table 1). The decreased O_2 levels may result in a faster transition from aerobic to anaerobic respiration, lower tolerance for physical exertion, and decreased working capacity (Laferty and McKay, 2006). It should be noted that despite the decrease in O_2% in the RPD cavity, no impact on blood oxygen saturation (SpO_2), as measured via pulse oximetry, was found in both the abovementioned studies. This discrepancy could plausibly be related to a brief period of RPD use during low energy expenditure, as suggested by a study that found a significant decrease in SpO_2 in surgeons wearing SMs only during procedures longer than 1 h (Beder et al., 2008) and another reporting a significant decline of arterial partial pressure of O_2 in patients wearing N95 FFRs after 4 h of hemodialysis (Kao et al., 2004).

1.2. Implications of RPD-related respiratory effects for panic pathophysiology

Considering the pathophysiology of panic, these RPD respiratory effects may have a peculiar and relevant impact on vulnerable individuals. Patients with PD were thought to have a hyperactive suffocation alarm, which results in a specific behavioral and respiratory hypersensitivity to hypercapnia (Klein, 1993). Different laboratory challenges inducing hypercapnia, such as the Read rebreathing technique, the prolonged inhalation of 5% or 7% CO_2-enriched air, or the double inhalation of a 35% CO_2/65% O_2 gas mixture, induce significantly higher rates of PAs, with pronounced respiratory symptoms in patients with PD compared with control groups (Caldirola and Perna, 2019; Gorman et al., 1997; Leibold et al., 2016; Okuro et al., 2020; Perna et al., 1999). Similarly, individuals who experienced PAs without developing full-blown PD and healthy first-degree relatives of patients with PD displayed greater likelihood of panic symptoms and respiratory-response abnormalities during hypercapnic challenges than the control group (Caldirola and Perna, 2019). Moreover, patients with PD are hypersensitive to other laboratory respiratory challenges, such as breath-holding, hyperventilation, or a hypoxic challenge test (Beck et al., 1999; Caldirola and Perna, 2019; Okuro et al., 2020). They suffer from irregular breathing patterns, impaired diaphragmatic breathing with reduced vital capacity, chronic hyperventilation, and a common sensation of difficulty in breathing during daily life activities (Caldirola and Perna, 2019; Grassi et al., 2013). Hence, it is conceivable that the inhalation of increased CO_2 concentrations while wearing RPDs may elicit respiratory discomfort, a sense of suffocation, and panic symptoms to a larger extent in panic-prone individuals than in others. They may also be more sensitive to increased breathing resistance and decreased concentrations of inhaled O_2 than nonpanic-prone individuals, resulting in greater breathing effort, dyspnea and physical fatigue, even during mild physical activity. The greater-than-expected associations between PD and asthma/chronic obstructive pulmonary disease (Goodwin and Eaton, 2003; Hasler et al., 2005) may further increase the risk of RPD-related respiratory and physical discomfort in panic-prone individuals.

The use of RPDs has also been associated with other physiological effects, such as disturbances in visual performance, which is thought to cause disorientation in the environment. Other effects include increased air temperature in the RPD cavity (up to approximately 32°C–33°C) with sweat accumulation, which may add a further burden to breathing and general discomfort (Johnson, 2016; Zhang et al., 2016). Individuals vulnerable to panic exhibited higher postural instability and dizziness when exposed to unusual patterns of visuo-vestibular interactions and imbalanced autonomic regulation with reduced heart rate variability (Caldirola et al., 2011; Caldirola and Perna, 2019; Coelho and Balaban, 2015; Zhang et al., 2020). Thus, these individuals may also be more sensitive to the additional non-respiratory and physiological burdens related to FFR use.

1.3. Limitations and conclusions

This research presents some limitations. Despite the extensive use of the RPDs, the body of research studying the objective physiological impact of wearing these devices was relatively limited. Most studies included small samples, with a preponderance of young participants, thereby limiting the generalizability to other populations. Furthermore, different methodologies and experimental conditions were used across studies, which may explain some differences in results. Finally, as the studies were conducted in laboratory settings, the ecological validity of the results is not clear-cut, and possible differences between results obtained in experimental settings and physical responses when wearing RPDs in daily life cannot be excluded.

Taking these limitations into consideration, this research supports the idea that individuals vulnerable to panic may be at higher risk of relevant discomfort while wearing RPDs, thereby reducing their tolerance for these devices, as we have observed in our current clinical practice. For this reason, these individuals may be poorly compliant in their use, increasing their risk of contracting COVID-19. Therefore, a "panic fitness" evaluation for the use of respirators should be considered in different settings, including the workplace, and strategies to decrease discomfort should be identified to increase the rate of compliance. It is noteworthy that in some questionnaires used in the process of medical clearance prior to respirator use, screening for the presence of claustrophobia, a condition often associated with PAs and PD, has been included (Desautels et al., 2016; Pappas et al., 1999). Example strategies to increase compliance in individuals vulnerable to panic may include repeated recovery periods in safe conditions during which RPDs are not used and a personalized approach to workload based on the respirator tolerance of individuals. Moreover, the most suitable type of RPDs should be chosen for panic-prone individuals, while remaining within safety recommendations based on the context in which the devices are used and the level of risk. For example, the physiological effects of RPDs described above refer to the use of FFRs, while preliminary results show that compared with N95 FFRs, SMs resulted in a lower absolute humidity inside the mask and were associated with a lower subjective perception of humidity, heat, breathing resistance, and overall discomfort (Li et al., 2005). Thus, SMs may be more tolerable for individuals vulnerable to panic, although further studies on the physiological effects of SMs are needed for confirmation. Furthermore, novel N95 FFRs with micro fans or elastomeric respirators with breathing system filters, might be useful alternatives because these devices are able to better maintain physiological CO_2 levels during use (Goh et al., 2019; Liu et al., 2020).

More research is clearly necessary to draw reliable conclusions on the connection between RPDs and panic. However, considering the ongoing COVID-19 pandemic and the substantial prevalence of panic vulnerability [the prevalence of PD is approximately 3.8% in the US and European general population, while that of subthreshold panic is similar or even higher (Kessler et al., 2012)], this issue is worthy of consideration for its potential impact on public health.

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Giampaolo Perna has served as consultant for Lundbeck, Menarini and Pfizer.

CRediT authorship contribution statement

Giampaolo Perna: Conceptualization, Methodology, Supervision,

Writing - review & editing. **Francesco Cuniberti:** Writing - original draft. **Silvia Daccò:** Writing - original draft. **Maria Nobile:** Methodology, Writing - review & editing. **Daniela Caldirola:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

All other authors declare that they have no conflicts of interest.

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