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Editorial

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From Pandemic to World Instability and War Crimes: Lessons Learned in a Turbulent Socio-Political Landscape

The COVID-19 pandemic has been a transformative event in our lives, impacting every aspect of society. Corradi and Ranzieri provides an overview of articles published in our journal to deal with the multifaceted nature of this new disease. [1] They also suggest that COVID-19 has been a trigger further accelerating the change of paradigm of Occupational Medicine, which is more and more concerned with prevention, contributing to health promotion and Total Worker Health®. [1] Such an unprecedented crisis has also taught us valuable lessons that should guide us as we face similar challenges in the future. Two articles published in this issue provide an overview of the lessons learned during the first four years of living with SARS-CoV-2, which should help us be prepared for possible future pandemics [2, 3]. One of the most significant lessons of the pandemic is the importance of a robust and resilient healthcare system. The virus has exposed weaknesses in healthcare infrastructure, highlighting the need for investment in public healthcare. Governments worldwide have realized the importance of preparedness, early diagnosis, and rapid response to combat infectious diseases. However, cooperation between health workers, researchers, and policymakers — vital for effective crisis management — is now weaker than ever.

Another lesson learned is the value of scientific research and evidence-based decision-making. The pandemic has demonstrated the importance of relying on scientific expertise and data when formulating policies and guidelines. It has also shown us the importance of effective communication between scientists and the public to build trust and ensure compliance with public health measures. The pandemic has underscored the significance of global collaboration in times of crisis to share knowledge, resources, and expertise to develop vaccines and treatments at an unprecedented pace. The speed at which multiple vaccines were created is a testament to what can be achieved through international cooperation. This lesson will be crucial in addressing future global challenges such as climate change or pandemics. Nevertheless, especially when the pandemic was over, loud anti-scientific no-vax groups stole the scene, taking over the stage in the media, sponsored by unscrupulous politicians in search of some more consensus. A recent European survey suggests that initiatives to counter misinformation are essential, encouraging health professionals and citizens to seek information from reliable government sources. [4].

On an individual level, the pandemic has taught us valuable lessons about personal resilience and adaptability. We have had to cope with changes in our daily routines, isolation from loved ones, financial hardships, and mental health challenges. The experience has emphasized the importance of self-care, mental wellness, and building strong support networks. We have witnessed a shift towards remote work and digitalization, accelerating technology adoption in various sectors, from education and healthcare to retail and entertainment. This has highlighted the importance of digital literacy and the need for equitable access to technology. The lessons learned from this experience will shape the future of work and education, leading to greater flexibility and innovation. Healthcare workers are the most critical asset within communities, particularly during crises resulting from a pandemic. Developing approaches that reduce burnout and focus on improving mental health and well-being is crucial in building our preparedness to face future pandemics [4].

The pandemic has also brought attention to existing social inequities and disparities. We have seen how specific communities, such as low-income individuals, minority groups, and frontline workers, have been disproportionately affected by the virus. This has prompted discussions about social justice, healthcare accessibility, and income inequality. We must address these systemic issues to create a fairer society. The pandemic has reminded us of the value of human connection and community, to support each other through virtual gatherings or acts of kindness. This lesson serves as a reminder that we are all interconnected and that our collective well-being depends on supporting one another with empathy and compassion toward those in need. Unfortunately, we must recognize we are facing the worst conflictual period since the end of World War II, as if the pandemic had disrupted global equilibria and fueled regional and international conflicts. The COVID-19 pandemic has exposed existing fault lines and geopolitical tensions, which can escalate into a world war if not adequately addressed. In a world that has survived the challenge of the pandemic, other economic and social crises have exploded, paving the way for resurgent nationalisms and winds of war, which make it increasingly challenging to confine conflicts to a regional scale.

Strained international relations and cooperation, blame games, finger-pointing, and a lack of coordination among nations characterized the initial response to the outbreak, but even more so, the end of the pandemic. The international lockdown measures and restrictions have resulted in severe economic downturns, job losses, and increased poverty levels. Financial hardships can create social unrest and exacerbate existing inequalities within societies. In such circumstances, there is a risk that countries may resort to protectionism, trade disputes, or other forms of economic warfare as they strive for self-reliance and security.

Moreover, the pandemic has strained international relations and cooperation. This lack of collaboration can further exacerbate geopolitical rivalries and fuel conflicts. In regions with existing tensions or territorial disputes, such as Eastern Europe, the South China Sea, or the Middle East, a fighting attitude and lack of collaboration can exacerbate geopolitical rivalries and fuel conflicts, disrupting global equilibria and favoring opportunistic actions or power plays. It is crucial to recognize these potential threats and war crimes associated with either aggression or disproportionate reactions and work towards mitigating them.

The lessons learned from the pandemic should inform global efforts to strengthen international institutions, promote multilateralism, and enhance cooperation. Countries must prioritize diplomacy, dialogue, and collaborative problem-solving over unilateral actions or aggression. The health crisis has strained resources such as medical supplies, vaccines, and essential commodities. When access to these resources becomes limited or politicized, there is a risk of increased competition or armed conflict over access to vital resources. Countries may prioritize their citizens' needs at the expense of others, leading to further geopolitical tension.

Another significant concern is how misinformation and disinformation during the pandemic can contribute to social polarization and foster mistrust among nations. False narratives regarding the origins of the virus or conspiracy theories can create divisions between countries and erode trust in international institutions. This erosion of trust may hinder diplomatic efforts to resolve conflicts peacefully or impede cooperation in public health or climate change areas.

In conclusion, while the COVID-19 pandemic has taught us valuable lessons in resilience and preparedness, it has also exposed vulnerabilities that have the potential to disrupt global equilibria and fuel regional and global conflicts. By recognizing these risks and taking proactive measures to address them, we can strive for a more peaceful and stable world in the aftermath of this crisis. International cooperation, diplomacy, and efforts towards social justice will be essential in navigating these challenges effectively. After World War II, sharing resources and international collaboration resulted in Europe's most extended peaceful period, progressing toward a strengthened Union, which brought wealth, freedom, and better living conditions, which in recent years were troubled by resurgent nationalisms. Lessons learned with the pandemic should give a new impetus to efforts to build up and reinforce a large community struggling for health, peace, and prosperity in European countries and worldwide.

Antonio Mutti

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Reviews, Commentaries, Perspectives

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COVID-19 Marked a Change in the Scope of Occupational Medicine from Occupational to Work-Related Diseases and Total Worker Health®

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Keywords: Occupational Health; Infectious Diseases; Working Settings

Summary
The COVID-19 pandemic challenged Occupational Medicine, while its focus had already shifted from occupational diseases to work-related illnesses. Such a broader scope allowed the inclusion of transmissible diseases among the causes for concern in working settings. COVID-19 has had a profound impact globally, resulting in millions of infections, often lethal. From its appearance, COVID-19 was found to affect specific groups of workers at higher risk of contracting the virus due to their occupation or workplace conditions, which accounts for its consideration as a potential work-related disease. This overview examines various aspects of COVID-19 based on articles published in our journal. Specifically, the epidemiology of COVID-19 is discussed, including mortality rates and groups at higher risk. The diagnosis, measures to prevent contagion, vaccination efforts, long-term effects, and psychosocial factors are also summarized. The emerging picture is that COVID-19 has been a trigger accelerating the change of paradigm of occupational medicine, which is more and more concerned with prevention. Occupational Health contributes to health promotion and Total Worker Health®.

1. Introduction

Occupational Health has witnessed a significant change in paradigm over the years, shifting from a focus on occupational medicine to a comprehensive approach known as Total Worker Health® (TWH). This transition has been driven by recognizing that work-related diseases gradually replaced occupational diseases in the discipline's scope. This has led to the unprecedented inclusion of COVID-19 as a significant concern for occupational health [1].

Amid a new and potentially lethal infectious disease affecting all strata of the general population, and the first report covering the 1st semester of 2020 reporting an 11.1% excess mortality in Italy and an almost 50% excess in Lombardy, the most affected region, we decided to publish a series of papers monitoring mortality because of its relevant implications for controlling the time-course of the COVID-19 pandemic [2]. Social distancing, facial masks, and other measures that aimed at preventing COVID-19 also prevented the usual influenza epidemics in 2021; nevertheless, a 7.9% excess mortality was observed; of these deaths, 3,667 occurred among individuals of working age (25-64 years) [3]. In the 2020-2022 triennium, 225,965 deaths exceeded expected rates, and 16,017 of these occurred in working age [4-7]. Data on total mortality for the first half of 2023 suggested a rebound due to harvesting in previous years, 6,947 and 1,879 lower

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than expected in the general population and working age, respectively [8]. Increased mortality during the COVID-19 pandemic period could be due to delayed or missing access to treatment of highly prevalent chronic diseases, such as cardiovascular diseases, cancer, and diabetes, as well as to other factors such as fear of facing contact with other people and attending crowded places, and social anxiety [9].

2. Groups at Higher Risk

Occupational Medicine is critical in identifying vulnerable workers during pandemics, as it actually did during Sars-CoV-2 pandemics. A series of articles have highlighted specific occupational groups that face an increased risk of infection due to their proximity to infected individuals or their involvement in essential services. Individuals working in crowded and confined environments, such as taxi and bus drivers, have shown to be more susceptible to exposure. Healthcare workers, first responders, and frontline workers have also been identified as groups at higher risk, which justifies labeling COVID-19 as a work-related disease [10-12].

3. Diagnosis

The accurate and timely diagnosis of COVID-19 is paramount for effective disease management and prevention of further transmission. Various diagnostic methods, such as PCR antigen and antibody testing for diagnosing COVID-19 cases, have been discussed to improve their use and to choose the best one among available technologies, depending on the application context, to help occupational health professionals safeguard workers' health [13-17].

4. Measures to Prevent Contagion

Preventing the spread of COVID-19 within workplaces is crucial to protect workers and maintain business continuity. Efforts to implement preventive measures such as personal protective equipment (PPE), social distancing, improved ventilation systems, and sanitization protocols emphasized the importance of comprehensive infection control strategies within occupational settings. [18-20] Understanding the modality of transmission and ruling out seemingly obvious pathways has been essential to focus prevention measures [21].

As the pandemic evolves, new variants of SARS-CoV-2 keep emerging, with potentially different levels of virulence and lethality. Articles published in this journal have addressed these variations within the pandemic scenario, providing insights into their impact on workers' health. Occupational medicine must promptly adapt to evolving strains to ensure adequate risk assessment and management strategies.

5. Vaccination Efforts

The COVID-19 pandemic has posed an unprecedented challenge to global health, economies, and societies. However, amidst the chaos, the rapid development and deployment of effective vaccines have emerged as a game-changer strategy in our fight against the virus. Vaccines have been pivotal in mitigating the impact of the pandemic, promoting population's immunity, and favoring the diffusion of more contagious but less lethal variants of SARS-CoV-2 [22]. Occupational health practitioners played a relevant role in promoting vaccination acceptance and implementation among workers. This contributed to minimizing workplace transmission risks, owing to vaccine efficacy, safety, and effective distribution strategies [23-27].

6. Psychosocial Factors

While the initial focus has been on acute infection and mortality rates, understanding the long-term effects of COVID-19 is essential for managing occupational health. Persistent symptoms experienced by individuals who have recovered from the acute phase emphasize the need for long-term monitoring of affected workers, especially during the back-to-work phase [28-30].

Psychosocial factors associated with COVID-19 at the workplace or distance working can significantly impact employees' well-being and mental health. The sudden shift to remote work or changes in responsibilities and procedures due to the pandemic often led to increased workload and job demands. This has been able to cause stress (including technostress), burnout, and decreased job satisfaction [31, 32].

Balancing work responsibilities with personal life has often been challenging during the pandemic, especially when working from home. The boundaries between work and personal life has sometimes become blurred, leading to increased stress and difficulty in disconnecting from work. Remote work can result in social isolation and reduced opportunities for social interaction with colleagues. Lack of social support and limited communication can impact mental well-being and increase feelings of loneliness. Remote work may present challenges in effective communication, collaboration, and teamwork. Miscommunication or difficulties in getting timely responses from supervisors or colleagues can hinder productivity and create frustration among employees [33, 34]. Dependence on technology for remote work can lead to technical difficulties, connectivity issues, or inadequate infrastructure support, including issues related to the environment in which work occurs, originally not designed for that purpose. These challenges, particularly difficult to manage by occupational physicians, could add further strain on employees' mental well-being [34].

COVID-19 has completed the transition of the scope of Occupational Medicine from primarily addressing occupational diseases to encompassing a much wider veriety of work-related illnesses. Articles published in our journal provided valuable insights into various aspects of this challenging disease. From epidemiological studies to high-risk groups identification, effective diagnostic methods, preventive measures, vaccination efforts, long-term effects monitoring, and considerations regarding changes in virulence and lethality, but above all the duration of SARS-CoV-2 shedding and infectivity in working populations [35], these articles underscore the critical role that occupational medicine plays during a global pandemic like COVID-19.

Where applied, the traditional principles of public or occupational health already applied to protect workers from air pollution in several working settings, e.g., in mines, metallurgies, chemical industries – otherwise flawed and often overlooked – proved to be effective in controlling infection spreading [36, 37]. Therefore, it is important implementing these principles to ensure clean air in workplaces and other settings, leaving facial masks as a last resort to protect against infections.

7. Conclusions

The rapid development of effective COVID-19 vaccines is a testament to human resilience, scientific advancements, and global collaboration. It has provided us with a powerful tool to combat the struggles imposed by this deadly virus. Through accelerated vaccine development processes, stringent clinical trials, global collaboration efforts, and successful vaccination campaigns, we are now on the path toward recovery. However, it is essential to continue addressing vaccine hesitancy, ensuring equitable distribution worldwide, monitoring virus variants vigilantly, and adapting vaccination strategies accordingly. Occupational physicians are playing a new Public Health role. The paradigm shifts from occupational diseases to TWH® – embracing work-related disorders as an intermediate step to broaden the scope of Occupational Medicine – and this is a crucial milestone for Occupational Health [38]. The inclusion of COVID-19 as a work-related disease has also highlighted the need for a comprehensive approach that addresses not only physical health but also mental and social well-being. By embracing health promotion in the framework of TWH®, occupational health professionals can create safer and healthier workplaces, ultimately benefiting employees and organizations.

Declaration of Interest: The Authors declare no conflict of interest.

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Reviews, Commentaries, Perspectives

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COVID-19 in Workplace Settings: Lessons Learned for Occupational Medicine in the UK

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Keywords: SARS-CoV-2; Workers; Health; Airborne; Ventilation; Respiratory Protective Equipment

Summary

This paper addresses lessons learned from the COVID-19 pandemic from a UK Occupational Medicine perspective to permit comparison with other national accounts. In spite of good prior research and statute, the necessary resources to protect workers' health were seriously lacking when the pandemic struck. Weak public health guidance, which did not recognise dominant airborne transmission, was applied to workplaces, leaving workers and others unprotected, especially in respect of Respiratory Protective Equipment (RPE). The Health and Safety Executive (HSE) as regulator was lacking, for example, in not producing guidance to protect HealthCare Workers (HCW) who were amongst the most at risk. The UK COVID-19 Public Inquiry should address shortcomings such as these, but recommendations must be accompanied by robust means to ensure appropriate implementation. These should range from substantial measures to improve indoor air quality, to a permanent pandemic management organization with adequate resources. The enforcing authority has to be obliged to publish more specific workplace guidance than the public health authorities. Occupational Medicine as a discipline needs to be better prepared, and hence to assert its responsibility towards high standards of workers' health protection. Future research has to include investigating the best means of mitigation against airborne infection and the management of post-acute covid sequelae.

1. Introduction

The COVID-19 pandemic has taken a terrible toll through death and ill health in workers. Self-reported data indicate that 123,000 workers in 2021/22 in Great Britain were suffering from COVID-19, which they believed may have been from new or long-standing exposure to the coronavirus (SARS-CoV-2) at work. A further 585,000 reported that they were suffering from a work-related illness caused or made worse by the effects of the COVID-19 pandemic [1]. Moreover, the pandemic resulted in other damage ranging from economic cost to negative attitudes toward the acceptability of occupational risk. Serious questions are being raised about how well the pandemic was managed in its first three years and how its enduring legacy is being handled [2]. The main aim of this perspective is to contribute to the important debate about Occupational Health aspects of the COVID-19 pandemic in the UK to learn lessons arising from this pandemic for potential future public and Occupational Health crises.

It is recognised that there are many controversial issues and diverging opinions even when considering the pandemic from only the standpoint of the UK. To permit a comparative exercise alongside national perspectives in this journal and elsewhere, salient themes have been addressed in the following editorially defined template and sequence.

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2. Main Occupational Health Challenges During the COVID-19 Pandemic

At the basic level of Occupational Health delivery, the main challenges were that in spite of prior scientific knowledge, UK government preparation was pathetic; the official narrative advocated measures directed against non-dominant modes of transmission (e.g., fomites) while practically ignoring airborne transmission (aerosols). Inadequate source, pathway, and receptor controls resulted in a burden of occupational disease, which should have been avoided [3]. Aspects of these challenges are explored in more detail in other sections below.

Depiction of health and the economy at opposite ends of a see-saw in a zero-sum game risk mistakenly oversimplifying the complex and dynamic interaction between the two. Government's attitudes and actions in the UK often appeared to be based on a naive assumption that workers and other people might have to die for the economy to flourish [4]. A comprehensive appraisal of the costs and benefits of a range of options for risk mitigation in workplaces and other settings is beyond the scope of this account and, to an extent, premature. However, evidence is mounting. For example, the UK Government's "Eat Out to Help Out Scheme" in August 2020 gave 50% subsidies for meals inside restaurants at a cost of about £850m to taxpayers. The scheme, in common with some other UK government COVID-19 interventions, was launched without consultation with public health authorities [5] and diverged from policy in other countries. A study suggested that this scheme may have been responsible for 8% to 17% of all newly detected COVID-19 infections late that summer and accelerated the second COVID-19 wave [6]. This raises a question about the extent to which an alternative investment in measures such as ventilation and particulate air filtration might have had a net positive cumulative effect on the economy and also prevented many hospitality workers and other people from contracting COVID-19. Perhaps as more analyses are undertaken, we may yet conclude that a lockdown in a pandemic is as appropriate a response as an emergency laparotomy in a patient *in extremis* suffering from a perforated peptic ulcer. If the underlying condition had been better managed earlier, such an intervention might never have been needed. The UK Government prevaricated instead of learning from the Italian experience, and its conduct in the pandemic was recently labelled "criminal incompetence" by The Lancet, which stated that "many, if not most, of over 230,000 deaths were preventable" [7].

About 1.7 million people in the UK have self-reported Long COVID symptoms at least 12 weeks post-infection. As a proportion of the UK population, the prevalence of self-reported Long COVID was greatest in people aged 35 to 69 years [8]. Appraisal and interpretation of the epidemiologic evidence laid before the UK Parliament suggests that a substantial portion of this morbidity was caused by work [9]. Moreover, various studies show the effects on well-being in occupational groups. For instance, in a survey of UK doctors with Long COVID, more than 55% of whom had contracted the disease in 2020, one-fifth of respondents were still unable to work at the end of 2022 due to long-term sickness [10].

The direct impacts of the pandemic and its management are an important focus of the UK's COVID-19 Public Inquiry. However, the indications are that the COVID-19 pandemic in the UK exposed and amplified inherent weaknesses in the health service to an extent that could have been largely avoided had the service been more resilient and better resourced prior to the pandemic [11].

3. Occupational Settings, Transmission of COVID-19, and Measures Mitigating This Risk

Extensive research has been undertaken in the UK regarding the associations between the risk of contracting COVID-19 and work across industrial sectors and occupations, as appraised by the Industrial Injuries Advisory Council [9]. In large studies, significantly elevated mortality rates (involving COVID-19) were found in a range of occupations, such as in health and social care, as well as taxi and bus drivers. These elevated rates tended to remain significant (though attenuated) even after adjustment for confounding factors including ethnicity, education, deprivation, or prepandemic health [12, 13]. Infection studies showed comparable results in these occupations but also in others such as education [14]. Other studies investigating SARS-CoV-2 infection as an outcome also showed significantly increased relative risks associated with occupation, such as 8.7 in health care support staff and 2.2 in transport workers [15]. Another study of the risk of infection in the first wave of the pandemic adjusted for age, gender, ethnicity, social deprivation and co-morbidity, focussing on 158,445 health care workers (HCW) and 229,905 members of their households. Besides showing significantly increased relative risks for HCW whether compared to the general population or to members of their household, the study showed that 'front door' HCW had double the risk of (the usually better protected) staff in Intensive Therapy Units [16].

Research into occupational transmission of COVID-19 and mitigation in the UK is being undertaken as part of a national programme [17] as well as several independent initiatives. In general, the findings are consistent with the extant strong evidence of airborne transmission of COVID-19 being predominant [18] as was the case with other earlier recognised beta-coronaviruses. Illustrations of research in UK occupational settings included a time series study of COVID-19 infections in health care workers (HCW) showing the efficacy of FFP3 respirators (replacing surgical masks) in controlling nosocomial infection of hospital staff [19]. Other studies aimed at mitigating the pathway of transmission. For instance, supplementary high-efficiency particulate air filtration was shown to attenuate a range of airborne fine particulate matter fractions [20]. Clearly the advent of vaccines considerably reduced the burden of COVID-19 in occupational settings as they did in the community at large, but vaccines should not be considered a substitute for other measures to mitigate risk [3].

4. Key Lessons in Protecting Workers' Health and Safety in Occupational Settings

Even without waiting for the final findings of the COVID-19 Public Inquiry several key lessons have been clear. The favourable pandemic preparedness rank [21] that the UK had in 2019 was based on scientific knowledge, exercises, and policies that had not been implemented when COVID-19 struck [3, 22]. At the onset of the pandemic, the UK Government had other priorities and did not treat worker protection with the measures it deserved [23]. The Government did not include accredited specialists in all the appropriate disciplines, such as Occupational Medicine and Occupational Hygiene, in its topmost advisory groups dealing with the emergency, and often ignored such expertise as it did have [5]. The authorities did not heed recommendations for a precautionary approach to worker protection, especially concerning Respiratory Protective Equipment (RPE), when these were made early in the pandemic by academics [24] or by occupational hygiene bodies [25] recommending control banding based on the 'source-pathway-receptor' model [26]. However, even medical experts need to learn lessons since although the COVID-19 crisis was caused by a 'disease', randomised controlled trials, which are usually the gold standard for evidence of medical treatment, are not the key methods for testing engineering and other measures of pathway and receptor control [27].

Finally, at the level of worker protection, the biggest shortcoming was the denial of the predominantly airborne transmission of the SARS-CoV-2 virus [18, 22]. These clear lessons have not yet been learned [3]. Thus, the current official infection prevention and control 'manual' does not explicitly recommend Respiratory Protective Equipment (RPE) for HCWs who are vulnerable through potential exposure to COVID-19 in routine clinical care nor for individuals who may have increased susceptibility because of risk factors such as immunodeficiency [28]. The manual remains wedded to the concept of Aerosol Generating Procedures (AGPs) even though good evidence has shown that they tend to be less likely to generate aerosols than coughing or mere breathing, and they have therefore been discredited as means of categorising exposure to determine the need for RPE [29].

5. Respiratory Protective Equipment

First and foremost, it is worth recollecting the assertions of the founder president of the Institute of Occupational Hygienists (UK) and a previous president of the British Occupational Hygiene Society [30]. These words are just as valid for COVID-19 as they were in the context of when they were first written:

«There is no question that respirators […] should serve as the last line of defence against excessive exposure […] but there are nevertheless plenty of jobs in which they can and should be used freely, not as a substitute for engineering control but as a necessary adjunct. Respirators enable jobs to be done which could not be done without them».

In 2008, long before the COVID-19 pandemic, researchers at the Health and Safety Laboratory of the Health and Safety Executive (HSE) in the UK summarised the state of prior knowledge saying that it is a «common misperception … that surgical masks will protect against aerosols» [31]. In well-designed experiments they showed that «Live viruses could be detected in the air behind all surgical masks tested. By contrast, properly fitted respirators could provide at least a 100-fold reduction». Very presciently, they also stated that «The widespread use of respirators might be difficult to sustain during a pandemic unless provision is made for their use in advance». Good empirical evidence grounded in basic science, such as aerosol physics, has served to effectively protect millions of workers worldwide such as coal miners, and asbestos and construction workers. As regards biological agents, HSE guidance stated that «When in an airborne state, micro-organisms can be classed as particles, so they can usually be removed by filter-type RPE. You should always use equipment fitted with the highest efficiency filter possible (protection factor of at least 20)» [32].

The role of respirators as RPE for HCW in the routine clinical care of patients infected with SARS-Coronaviruses was accepted by a consensus of UK infectious disease and health and safety experts well in advance of the COVID-19 pandemic [33]. Comparisons of surgical masks and respirators have been the subject of much controversy, but it is important to correctly interpret appropriate studies to recognise respirators as essential for worker protection [27, 34]. Although respirators should be the default RPE, depending on a risk assessment, the same clinical task may warrant different types of respirators or even none at all [3]. In order to reduce condensation and discomfort for the wearer, circumstances may dictate the wearing of respirators with an exhalation valve, but even in these circumstances, the valved respirator is likely to afford as much source control as a surgical mask [35]. Respirators may cause dermatoses which are treatable [36] or, better still, preventable [37]. Alternatives include elastomeric respirators, and powered air purifying respirators (PAPR) [38] which deserve more consideration especially having less likelihood of skin reactions, being probably more 'sustainable' and costing no more than a mobile phone.

During the COVID-19 pandemic, HCW in the UK and elsewhere were presented with the narrative that surgical masks were effective PPE or RPE. This was probably prompted by the concern that their provision was grossly inadequate, as warnings prior to the pandemic had not been heeded [31, 39, 40]. Surgical masks have never met standards for RPE, though they may protect against fluid splashes. This is not to say that such masks do not provide some measure of attenuation of risk just as practically any footwear would protect otherwise bare feet in a construction site from injury to a very limited degree – but not any shoes are 'safety boots'. Regrettably the unproven belief that fomites were a substantial mode of transmission of COVID-19 coupled with an ignorance of how respirator filters work, stifled informed debate on respirator re-use.

6. Vulnerabilities and Inequalities in Occupational Health

The worldwide literature has shown that the risk of COVID-19 mortality is increased further in those people with a prior increased risk of dying, usually associated with increasing age, body mass index or comorbidity such as diabetes, as well as other factors such as male gender. During the COVID-19 pandemic many of these people were ignored [41]. Early in the COVID-19 pandemic, members of the UK Occupational Medicine community developed a model to quantify risks associated with specific comorbidities and other factors by expressing these as "equivalent years of added age" and thus assist decisions on occupational placement of workers [42]. At a wider population level, mortality studies in the UK using different methods [12, 13] showed that a large part of the crude mortality rate associated with occupation can be accounted for by variables such as socioeconomic deprivation, ethnicity, and comorbidity. However, the data warrant careful interpretation since many 'vulnerabilities' and 'inequalities' are associated with an increased likelihood of exposure to COVID-19 at work or elsewhere [12]. Sadly, during the COVID-19 pandemic, the deaths of many HCWs and other essential workers appeared to be explained away because they had 'underlying factors' such as a comorbidity (which often did not affect their fitness for work and had minimal consequence for their quality of life and expectancy). This narrative deflected concern from the 'necessary cause' of their demise namely exposure to SARS-CoV-2 (often with inadequate protection) [3].

7. Occupational Health Principles to Prevent Transmission in Workplace Settings

Contrary to beliefs before the pandemic and in common with some other Western countries, the national UK pandemic control systems were very disappointing in their performance when compared to prior expectations in 2019 [21]. However, this did not happen fundamentally because the basic principles of public or Occupational Health, as traditionally taught by and to practitioners in this area, were flawed. Rather, the failures arose firstly because of prior under-investment [3, 11, 43, 44]. Secondly public as well as Occupational Health principles were ignored or overridden [5, 7, 40, 41]. Instead of fatalism, the country needed a determination to find ways and means to practise traditional principles of Public Health and Occupational Hygiene, especially by using national resources to provide and mandate clean air in workplaces and elsewhere, together with specific measures to protect workers [3, 23].

The ethos of Occupational Health protection in the UK is to ensure health (at work) in the words of the law "so far as reasonably practicable" [45]. This means reducing the risk of ill health, whether or not the outcomes are likely fatal. Yet, at the onset of the pandemic, a decision ostensibly determined by infectious disease and public health experts considered the case fatality ratio of COVID-19 not bad enough to offer RPE to the vast majority of SARS-CoV-2 exposed HCWs [40]. Such an outlook on worker protection is alien to the good practice of Occupational Health. It would be tantamount to denying eye protection to welders, or hearing protection or safety boots to quarry workers on the grounds that blindness, deafness and crushed feet are not deemed fatal injuries. Another analogy might be made with occupational asthma. How would society react if workers exposed to asthmagens such as flour or diisocyanates were denied protection because "yes, the disease may be fatal sometimes, but not usually"? Occupational Health principles need to be reasserted as a robust response to the dangerous combination of death and ill health of workers caused by COVID-19 coupled with the fatalistic attitude demonstrated by many in authority and perhaps in society more generally.

8. Mental Health and Strategies to Support Resilience

Although the COVID-19 pandemic has had mental health consequences throughout the population, at the onset potential adverse mental health effects were a cause for concern especially for HCW [23]. In the UK, a survey shortly after the first COVID-19 pandemic peak showed that nearly a third of HCWs reported moderate to severe levels of anxiety and depression, and that more than four times as many reported very high symptom scores than pre-pandemic [46].

Various studies addressed specific occupations; thus, in an investigation of 'Burnout' in trainee/junior doctors, 6 of the 10 highest-rated stressors were specific to the COVID-19 pandemic, with several strong associations with Emotional Exhaustion, as well as Depersonalisation and (reduced) Personal Accomplishment [47].

Sadly, one can expect an adverse legacy on mental health as well as on physical health, as a result of post-acute COVID-19 or Long COVID [10]. Considerable investment needs to be made in a national strategy to protect and promote health, in the clinical management of these sufferers and in their occupational rehabilitation. In the tradition of Occupational Medicine, emphasis has to be placed on resilient workplaces and work practices at the organisational and environmental level with approaches such as communication, information and training, improvement in teamwork, working patterns and conditions, as well as individual support [48].

9. Implications of Teleworking

The effect of homeworking on health and productivity is very complex, with many mediating and moderating factors. Therefore, a consensus, even at a national level, still needs to be achieved. A systematic review based on 27 eligible studies from the UK and other OECD countries showed that those starting homeworking for the first time during the pandemic and those with poor mental health were, perhaps unsurprisingly, at risk of poor productivity [49]. One may have to wait for clear new strategies to emerge, although there have been several helpful indications. For example, occasional remote working from home might have net benefits, whereas the overall consequences of continuously working from home might be negative, especially on mental well-being [50].

10. Occupational Health Guidelines and Regulatory Framework

There have been calls to tighten the UK's regulatory framework based on lessons learned from the COVID-19 pandemic, and some changes in statute might indeed be warranted. However, the major failings during the pandemic did not arise from shortcomings in extant regulatory frameworks but from failures in complying with the law as it stands, in providing correct official guidance, and in enforcement [45]. In the UK, Health and Safety Law applies not only to workers but essentially to all people in workplaces including for example patients in hospitals, residents in old people's homes and pupils or students at school. They have all been let down and as has been cogently argued, it is now difficult to avoid the conclusion that there has been an "unwillingness on the part of the state to effectively address the blatant and repeated failure of duty-holders to manage workplace exposure to COVID-19 according to well-established principles of good practice and basic regulatory requirements" [43].

The HSE had a laudable record for publishing guidance to protect workers from hazards ranging from asbestos to Legionnaires' disease. Yet the HSE abrogated that responsibility in an unprecedented manner. Despite requests from trade unions representing nurses and doctors, the HSE refused to publish official evidence-based guidance or an "Approved Code of Practice" for the protection from COVID-19 of HCWs (or their counterparts in social care who have similar risks [9]). Instead, the HSE deferred to "effective control measures, as set out in the relevant Public Health England guidance", an assertion for which the HSE refused to provide evidence and conflicted with its prior evidence or assessment [31-33]. However, the HSE removed the assertion from its website after being questioned [51]. HCWs who took the personal initiative of buying respirators to protect themselves and their colleagues reported being threatened by their superiors. Eventually, healthcare trade unions resorted to producing their own guidelines on COVID-19 risk assessment [52, 53]. Besides UK Trade Unions, Nongovernmental Organisations also stepped in to make up for failures in Government [25, 44]. The experience of the COVID-19 pandemic prompts the question as to whether some obligations to ensure health and safety should additionally be statutorily imposed on the government and its agencies, such as the HSE.

Such generic guidance that the HSE produced was for workplaces other than health care, largely replicating public health guidance on behavioural safety [43] (such as hand washing and 'social distancing'). This HSE guidance did not emphasise legal obligations such as statutory reporting of COVID-19 cases suspected to have been contracted at work as per the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR) [54]. Over the period 10 April 2020 – 31 March 2022, employers made 44,458 official notifications to the enforcement authorities in Great

Britain of cases of COVID-19 in workers where there was reasonable evidence to suggest that it was caused by occupational exposure. These ranged across all industry sectors and included 459 fatalities [55]. However, the HSE guidance was flawed [50, 56], and there were gaps in data collection [55]. Widespread inconsistencies, such as in the distribution of these reports made by employers regarding HCW, suggest that there has been gross under-reporting despite the law [57].

11. National Services Versus Local Initiatives

A priori, centralising the development of guidance and policy as well as of resources, whether human or other assets, might appear to be the most efficient and effective approach. Once the guidance would be shared and applied universally and the resources distributed fairly one could thence hopefully achieve equity. However, in the UK, as was apparent early in the COVID-19 pandemic, this 'top down' approach resulted in waste through incompetence or corruption [58]. Moreover, as shown above, this centralised 'command and control' resulted in flawed policy and guidance specifically as regards the protection of workers.

Especially in crises such as the COVID-19 pandemic, the local knowledge and other attributes of primary and community healthcare systems, particularly in dealing with socioeconomic determinants, have a crucial part to play [59]. Anecdotal and other evidence sources suggest that such beacons of good practice as were evident in some private Occupational Health service delivery or in some organisations in the public sector [19, 20] during the pandemic tended to arise from local initiatives, even if modest at times.

12. Management of COVID-19 Risks in Occupational Settings

As illustrated in the above sections, the UK generally has poorly managed COVID-19 risks in its occupational settings. As discussed earlier, lessons ostensibly learnt from previous pandemics turned out to have been ignored. Issues arising from a Coronavirus pandemic planning exercise in 2016 [39, 40], such as the provision of PPE and preparation of a video to teach HCW about RPE had not been acted upon. Within the wider public health context, the workplace and workforce were not given the specific protection warranted by their exposure and role [3]. High-risk work environments such as hospital wards did not get investment for improving their work environment through ventilation, nor were HCWs given adequate RPE. In other workplaces, minimal efforts were made, mainly focussed on fomite and droplet control. Generally, the HSE kept a low profile [43, 44] except perhaps in testing imports of PPE. On the positive side, multifaceted research programmes were launched [17], although this investment was minuscule compared to the several billion pounds of public funds which were wasted through incompetence and corruption [58].

13. Lessons Learnt

Important UK contributions to learning lessons will hopefully arise from the UK Public Inquiry chaired by a senior judge [4, 5, 7, 11, 41]. Although the final report will be years in the making, witness testimony so far suggests that it is on the right tracks to provide lessons to protect the health of workers and the general public from similar future threats. However, just as lessons learned following past outbreaks were forgotten [3, 22], there is a risk that the same failure in memory or implementation may follow the Inquiry. It will not be enough to say "we learned", but one must also commit to implementing those lessons and to give an iterative public and evidence-based account of what has been "learned". Therefore, robust solutions need to be found such as a specific pandemic organisation. Stakeholders and society in general need to be involved and have transparent reassurance on progress made through means such as regularly published reports, debates in Parliament, regular conferences, and other exercises. Although vaccines were a 'game changer', our paradigm in dealing with infectious hazards in the workplace has to shift from 'vaccines plus' to 'plus vaccines'. Thus, all reasonably practicable means in the control hierarchy must be implemented at the source, in the transmission pathway and at the 'receptor' [26] to protect workers before a vaccine becomes available to face a new threat [3].

History has taught us that step changes in preventing water-borne hazards were not primarily achieved by physicians but by engineers who oversaw the delivery of fresh, clean water and the safe disposal of effluent. Correspondingly, massive investment guided by appropriate expertise will be needed to achieve clean air in our workplaces and elsewhere [60]. Experts in health at work must be involved at the apex of national planning and decision-making. Occupational Health services, enforcement authorities, employers and employees must be well prepared in advance through attitude, resources and training to deal especially with airborne threats at source by interrupting transmission pathways as well as by using PPE, specifically RPE when and where appropriate [3].

14. Challenges and Opportunities for Future Research

Clearly, the pandemic has left us with a very long shopping list of future research needs, even in Occupational Health alone. Two salient but very different aspects will be highlighted by way of illustration.

Historical analogies with waterborne disease have already been made. Correspondingly, to protect workers and others from diseases caused by predominantly airborne pathogens such as SARS-CoV-2, a paradigm shift is needed [60]. Some of the research basis for this would be retrospective, based on the experience of employing ventilation, filtration and other measures during the COVID-19 pandemic. In contrast, other research would be prospective and experimental. Disciplines such as aerosol science, engineering and economics would be heavily involved. The aim would be to achieve the most cost-effective means of reducing risk to health while taking into account all relevant considerations such as comfort, productivity, affordability, sustainability and safeguarding the environment.

From a clinical perspective, the biggest challenge probably relates to the post-acute sequelae of COVID-19 infection. These range from an increased risk of various long-recognised clinical outcomes, such as myocardial infarction [9], to less well-defined outcomes, such as Long COVID. Both for the purposes of compensation and for case management the various phenotypes of the latter need better definition. For each of the distinct post-acute COVID-19 sequelae, research needs to establish not just the best methods of clinical management, but also of optimal occupational rehabilitation. Furthermore, well designed surveillance programmes and cohort studies are warranted to determine the possible risk of other outcomes such as damage to the immune system, and even neoplasia.

15. Conclusion

The COVID-19 pandemic was unprecedented in living memory in terms of magnitude and complexity. The virus, though novel as a species, transmitted itself similarly to others of the same genus. However, SARS-CoV-2 spread very rapidly in workplaces and in the community with an acute illness often manifest as a multisystem disease with serious sequelae including death. The UK response in workplaces, as elsewhere was often flawed and grossly inadequate. From the standpoint of Occupational Medicine, "following public health guidance" in the UK became a euphemism associated with neglect of the duty of care, of precautionary science and of good practice, such that workers, ranging from nurses to bus drivers, suffered needlessly. Therefore, the health of workers and within workplaces warranted specific considerations best handled by appropriate Occupational Health professionals, rather than being viewed as a mere setting within public health – especially when the latter's authorities may have been constrained by political influence. Within the disciplines important for Occupational Health, Aerosol Science and Occupational Hygiene generally endeavoured to make a significant contribution in protecting workers. Although the role of Occupational Medicine in managing individuals at risk of or from occupational disease is invaluable, it behoves occupational physicians to be even more proactive in preventing such disease in the first place.

Declaration of Interest: The Author declares that he is the elected representative for 'Occupational Medicine' on

the Council of the British Medical Association (BMA), and until recently, Co-Chair of the BMA Occupational Medicine Committee. He is also a member of the UK's Industrial Injuries Advisory Council. He was a Past President of the British Occupational Hygiene Society (The Chartered Society for Worker Health Protection), and a member of the Society's ad hoc working group on COVID-19 control measures. The opinions expressed in this article are solely those of the author.

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Learning from the Experience of the COVID-19 Pandemic: A New Paradigm for Occupational Biohazard Assessment and Management

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Summary

The COVID-19 pandemic has affected workplaces in many different aspects. In this scenario, Occupational Physicians played a crucial role in assessing and managing the risk of SARS-CoV-2 infection and associated disease to guarantee workers' health and the safety of workplaces. However, the pandemic experience has drawn attention to several critical issues in overall biohazard prevention and management strategies, originating from important knowledge gaps in our scientific understanding. An extensive analysis of the relevant hurdles that have emerged in our medical field can bring valuable lessons for the post-pandemic future, not only in preparation for possible new pathogens with pandemic potential but also with principles and concepts applicable to managing all biological agents. In particular, a paradigm shift is needed to properly approach occupational diseases caused by infective agents, accurately define the "case", assess exposure and possible causal relationship with work appropriately, and effectively manage the specific risk through implementing appropriate preventive and protective measures. In this framework, the Occupational Physician should expand his contribution based on his unique expertise and specific competencies, confirming his role as the go-to consultant in all occupational health matters, but also in a multidisciplinary approach, considering different scientific expertise and evidence.

1. Introduction

Since the start of the COVID-19 pandemic in March 2020, the occupational setting has been implicated by clusters of cases occurring in different workplaces. In particular, workers in close physical proximity with other people (e.g., coworkers, patients, users), in enclosed or shared spaces are more exposed and at a higher risk of COVID-19 in the absence of effective prevention and protection measures. At the European level, a preliminary analysis by the European Centre for Disease Prevention and Control (ECDC) indicated that most of the occupational clusters reported in the first six months of the pandemic took place in the healthcare sector but also in settings not traditionally considered to be at risk for transmissible biological agents, such as food packaging and processing, in factories and manufacturing, as well as in offices [1]. In addition, although with fewer clusters, cases were also reported from the mining sector, a context well known in the history of occupational medicine to be at risk for transmissible diseases, particularly tuberculosis and ancylostomiasis.

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At the Italian level, data from the *National Institute for Insurance against Injuries at Work* (INAIL) updated to May 2023 report that since the beginning of the pandemic, more than 320,000 COVID-19 infections have been notified due to occupational exposures, accounting for about one-sixth of the total number of all occupational injuries since January 2020. Although about half of these events occurred in the first pandemic year, the emergence of the Omicron variant, still prevalent at the time of writing, globally with its various subvariants, resulted in more than one-third of the total infections in 2022. Furthermore, Italian data indicate that healthcare was the most affected setting, with about 75% of all notified cases, in particular consisting of nurses (31.3%), aides (16.1%) and physicians (9.4%). However, other professional categories, such as administrative workers and professional drivers, followed with a proportion of 5.8% and 1.2%, respectively. The development, rapid production, and availability of effective vaccines as of December 2020 have resulted in a gradual but drastic reduction in adverse health outcomes among the workforce, as also observed in the general population. INAIL reports more than 900 deaths caused by occupational exposure to COVID-19, about two-thirds of which occurred in the first pandemic year, about one-third in 2021, and only 1 in 100 cases in 2022. Concerning overall mortality, although healthcare personnel were once again the most affected category, accounting for one-fourth of all fatal injuries, the analysis of specific jobs showed that administrative workers presented the highest proportion of fatal injuries (10.1%), followed by transportation workers (8.3%). In comparison, nurses (6.0%), physicians (4.8%) and aides (3.6%) demonstrated lower proportions [2].

From the perspective of applying a worker-oriented approach that could contribute to broader public health, Occupational Physicians have played a crucial role in reducing the risk of infection and possible complications in the workplace [3]. This involved not only individual risk assessment for susceptible workers and their appropriate placement in the workplace but also taking a range of preventive and protective measures to reduce health risks to employees, such as work adjustments, appropriate fitness-for-work assessments, implementing workplace vaccinations, as well as early identification and management of infected workers and close contacts. Additionally, an important role was performed in health assessments for the safe return to work of affected workers after recovery, not to mention the collaboration in the risk assessment of different occupational settings.

Indeed, workplaces have emerged as a critically important context of action as part of implementing and evaluating new preventive and protective strategies to counter the spread of SARS-CoV-2 infection. The rise in the appearance of new pathogens had raised the need for a paradigm shift in the management of biological risk, which, before the pandemic, was often considered to be of minor relevance to health and safety in the workplace of developed countries, restricting the focus mainly on the indisputable risk present in the healthcare, contact with animals and livestock and agricultural contexts. However, the pandemic experience has drawn attention to several critical issues in biohazard prevention and management strategies, stemming from important knowledge gaps which have severely limited the understanding of this phenomenon. A proper analysis of the significant concerns that have affected our medical field can bring valuable lessons for the post-pandemic future, not only in preparation for new emergencies of pathogens with pandemic potential but also with principles and concepts more broadly applicable to bio-risk management.

2. Case Definition of COVID-19

A crucial aspect that came into view immediately upon the emergence of this new pathogen was the case definition of COVID-19. From an initial clinical framing of severe respiratory infection, which led to the final naming of this new human coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), the rapid isolation of the virus meant that, within a few months, the sole necessary and sufficient criterion for pathological definition was the detection of viral material by RT-PCR [4]. The complete reliance of the diagnostics for COVID-19 on molecular identification of the virus effectively reduced the significance of clinical evaluation to irrelevance, which, for millennia, had always been the foundation for any diagnostic approach in medicine [5, 6]. Although, on the one hand, this approach was necessary for the rapid containment of infection and prevent potentially infected persons from spreading the virus in different human settings, on the other, it expanded the very concept of infectious "disease", thus diluting its meaning to a certain extent, in grouping completely asymptomatic positive subjects (who, we might infer, are infected but not ill), with issues with clinical pictures of acute respiratory infection, up to the more severe but characteristic bilateral interstitial pneumonia, into one single nosological category. In turn, this resulted in apparent flaws in managing the disease, unconcerned with the specificities of individual cases. For example, initial treatments were recommended without a proper risk-to-benefit ratio, with no consideration for disease severity or risk of adverse outcome in the specific individual case (e.g., prescription of hydroxychloroquine, exaggerated corticosteroid dosing) [7]. Additionally, the lack of knowledge of a precise pathogenetic mechanism of infection determined by SARS-CoV-2, or a characteristic clinical picture with specific signs and symptoms, produced a proliferation of associated syndromes involving various systems of the human organism, from dermatological syndromes to neurological alterations, bringing forth the risk for this disease to be classified into the historical set of "Great Pretenders", as was the case with tuberculosis and syphilis in the premodern era of medicine [8]. Over time, however, the accumulation of evidence in the scientific *corpus* has led the various medical branches to gain a greater understanding of the disease, improving clinical definition and, at the same time, tailoring therapeutic management to the individual case specificities, gradually overcoming, therefore, the initial *one-size-fits-all* approach [9].

3. Diagnostic Approach

In Occupational Medicine, the mentioned test-based approach brought significant benefits in rapidly managing contacts with prompt identification and isolation of incident cases, enabling the containment of infectious risks in the workplace. And yet, the blanket use of diagnostic tests, deprived of a critical assessment of each patient's clinical picture, can potentially reduce this diagnostic activity to a mere bureaucratic task of notifying cases to various institutions, as required by national laws and regulations. As suggested by the above INAIL data, although the extensive nationwide vaccination campaign has significantly reduced the clinical expression of COVID-19 in infected individuals, the Institute has recognised a relevant number of notifications as occupational injuries based on diagnoses obtained by detection of genetic or antigenic material. Furthermore, in addition to defining the "disease" of interest in Occupational Medicine, it is fundamental to understand its cause in relation to work. Indeed, identifying an occupational disease requires the nosological framing of the pathology and the etiological link with the specific occupation [10]. In this regard, a key criterion for verifying the occurrence of an occupational disease concerns temporality, which, in the case of infectious diseases, should consider the contagious period, the incubation time, and the serial interval between points. In the case of COVID-19, we found that the infectious period started around 1-2 days before clinical manifestations, the incubation period was equal to 3-5 days, and the serial interval was 4-5 days [11, 12]. As tricky as this verification may be during a pandemic, where any human setting could be considered a source of contagion, the methodological rigour of our medical speciality would allow, in many cases, if not most, to distinguish occupational cases from those acquired by other causes. Despite this, idle compliance with standard procedures mandated by law has enabled the uncritical reporting of PCR-positive subjects that were recognised by agencies by "simple presumption" of their occupational category (e.g., a healthcare worker that has COVID-19 is considered *ipso facto* occupationally acquired). The inevitable consequence of this "presumptive" diagnostic approach has been translated into a paradoxical prevalence of COVID-19 injury and illness reporting to insurance institutions. In contrast, in the pre-pandemic years, injuries caused by biohazards, and even during the pandemic years for all agents other than SARS-CoV-2, have always been characterised by a submergence of the problem. The pandemic experience, thus, reminds us that the diagnosis must be approached not only based on instrumental and laboratory documentation but must take into account the careful, specific assessment of the individual worker and the precise job, besides analysing the peculiar clinical conditions and exposure history in the workplace. Molecular or antigenic detection of viral material, while representing important supporting tools in the logical diagnostic process made by the Occupational Physician, nonetheless, cannot replace the necessary clinical reasoning on the individual worker but must complement it.

A further limitation carried by the exclusive reliance on diagnostic tests was observed in the indication of the end of isolation of the infected person for a safe return to work. During the early months of the pandemic, due to the lack of sufficient infectivity data and in the application of the "precautionary principle", leading international public health agencies linked the end of the infectious phase to the end of detection of viral RNA shedding, readily obtained through the wide availability of RT-PCR testing [13]. However, it is known that RNA can persist long after the end of the infectious phase for many viral diseases. The RNA shedding and infectivity intervals rarely coincide due to the immune response that neutralises different parts of the virus, preventing subsequent infection and progressively reducing its replication but not eliminating residual nucleic acid [14]. Therefore, PCR tests cannot effectively differentiate between shedding viable and potentially infectious virus or viral fragments. To date, the gold standard for assessment of viral infectivity is based on replication-compatible virus isolation on cell cultures [15]. Following the publication of evidence indicating that most infected individuals could not spread viable virus ten days after symptom onset and after clinical resolution in April 2020 [16], international health institutions modified their recommendations accordingly, ending the isolation of immunocompetent cases and discontinuing precautions around 10 days after clinical onset, allowing workers to return to work without the requirement of a negative RT-PCR result [17]. For public health purposes, the Italian Ministry of Health followed suit and applied a more conservative limit of 21 days from the onset of symptoms [18], which was more recently reduced to 5 days [19]; however, for return to work, the requirement of a negative antigen or RT-PCR test is still mandatory [19, 20]. Through a systematic review and meta-analysis [21], we showed that in immunocompetent workers, the average duration of RT-PCR positivity after the onset of symptoms was far longer (around 27 days) compared to the mean duration of SARS-CoV-2 infectivity (around 6 days). This secondary research, based on studies that assess both *in vivo* and *in vitro*, could be important in informing the assessment and management of COVID-19 risk in the workplace, applied in practice not only when evaluating clinically recovered individuals before their return to the workplace, but also to better assess and manage possible residual biological risks, to protect the health of the entire workforce.

4. Biohazard Risk Assessment and Management

The requirement of multiple levels of evidence, including virological evidence, raises a second additional important lesson taught by the pandemic, namely the important role of the various scientific disciplines necessary for appropriate and effective biohazard assessment and management. Indeed, the establishment of multidisciplinary teams with diverse expertise are needed to develop new procedures and tools aimed at reducing pathogen transmission. Specifically, in addition to Occupational Physicians, infection prevention and control (IPC) specialists, and industrial hygienists, who are the traditional actors involved in the management of biological risks in the workplace, new key figures such as engineers and physicists specialised in the fluid dynamics of disease transmission have emerged as an integral part of resolving significant issues in the control of infective risk in the workplace.

Indeed, the tools traditionally available for risk assessment and management, primarily following the hierarchy of controls, are important components of the well-known Anticipate, Recognize, Evaluate, Control, and Confirm (ARECC) reference model. This approach, however, was developed primarily for the control of chemical hazards and risks, thus requiring to be adapted to the specific characteristics of infectious pathogens, such as SARS-CoV-2. The identification of hazards and assessment of risks differs when evaluating biological agents versus chemical and physical agents [22]. While such models have been successfully applied to the deliberate biological use in specific workplaces (for which the exposure is planned due to work processes, e.g., microbiological laboratories), attempts to adapt them to the potential biological risk (for which the exposure is unplanned but could be foreseen, e.g., healthcare personnel), and specifically to the control of infectious disease outbreaks, are still limited. Biological risk assessment is further complicated because of the high level of variability in exposures, limitations in sampling methods, differences in the susceptibility of exposed individuals, as well as the lack of epidemiological data to support the identification of specific occupational exposure limits (OELs) [23]. Indeed, while chemical and physical agents are often evaluated on a quantitative basis, a qualitative or semi-quantitative approach is generally used for biological agents, such as the classification into "risk groups" identified by Directive 2000/54/EC of the European Parliament and Council and Article 268 Legislative Decree 81/2008, depending on the level of individual and community infection risk [24]. However, as well observed in the evolution of the recent pandemic, the assessment based on the aforementioned "risk groups" has not been matched by the actual biological risk, which evolves over time due to the changing epidemiological characteristics of pathogen spread in the community, the contagiousness and virulence of the circulating variant strains as well as the pharmacological interventions available. In fact, although SARS-CoV-2 has been included in Risk Group category 3 by the Commission Directive of the European Union 2020/739 since 3rd of June 2020, during the last phase of the pandemic we have seen an overall reduction of risk of severe disease due to acquired immunity through vaccinations or natural infection. This is quite evident analyzing the data on hospitalized patients and deaths between different pandemic waves provided by the Italian National Institute of Health, as the pandemic reached the endemic dimension [25]. Furthermore, in the presence of methodological limitations in exposure sampling, the assessment of occupational biological exposure is typically limited to qualitative characterisation (e.g., low, medium, and high): therefore, for an effective exposure assessment, it is appropriate to consider the mode of transmission of the pathogen as a key variable. In the absence of OELs, the concept of occupational exposure banding (OEB) has been borrowed from chemical assessment [26]. This approach relies on hazard-based data to identify an agent's infective potential and establish an environmental concentration range to place pathogens in categories according to infectious potential, virulence, and particle size distribution. Industrial hygienists and other experts in the field are in the developmental stages for the definition of appropriate OEB, which may lead to qualitative and semi-quantitative exposure metrics in the near future. In the current scenario, where important exposure variables may be missing, researchers have developed the strategy of control banding, a qualitative decision tool that allows Occupational Health professionals to identify for a particular job or task the degree of exposure to a specific hazard, combined with some measure of its toxicity. Integrating the two would allow the professional to individuate the appropriate control band for the particular job/task, guiding the proper type and nature of controls for that band. Applying these principles to an infective biological agent such as SARS-CoV-2, the definition of exposure would involve two main components: concentration and time. Without an adequate explanation of the former, the likelihood of encountering infectious sources during work has been proposed as a surrogate. Similarly, without toxicological data on specific pathogens, Risk Group could be used as a surrogate for toxicity. Combining these two variables can provide a control banding matrix that can effectively stratify the appropriate measures for different levels of exposure in different working groups and tasks [27].

From this perspective of controlling hazards and risks, it has been necessary to act on the multiple factors in the "chain of infection" to prevent viral transmission in occupational settings [22]. Indeed, pathogen exposures can be controlled within a framework that borrows from the classic industrial hygiene hierarchy of controls, particularly from the pathway-based approach applied to noise and radiation exposure, as suggested by Sietsema et al., who developed the conceptual model of "source, pathway, and receptor" [28]. At each of these levels, occupational health professionals can assess and manage risks based on the specific characteristics of the biological agent and disease, enacting control measures in order of efficacy at the source, at the pathway and finally at the worker level. During the pandemic, particularly in the early stages, many difficulties were met in rapidly identifying asymptomatic (or presymptomatic) infectious individuals, which comprise the source level. As detailed in studies published in the Journal, contagions have often occurred in the workplace from infective subjects with no clinical presentation, possibly due to low-risk perception, particularly during work breaks [29].

5. Modes of Transmission of SARS-CoV-2

At the pathway level, in the specific case of SARS-CoV-2, the main modes of transmission that have been studied over the years are the following, in order of epidemiological significance: i) inhalation of very fine respiratory droplets and aerosol particles, ii) deposition of respiratory droplets and particles on exposed mucous membranes of the mouth, nose, or eyes through direct splashes, and iii) contact with mucous membranes of hands contaminated either directly by respiratory fluids containing the virus or indirectly through surfaces. In this regard, one of the main lessons learned from the recent pandemic relates to the first two modes of transmission mentioned through the airborne pathway. Indeed, droplet and aerosol transmission should not be considered mutually exclusive but rather represent a spectrum in continuity that includes so-called close-range aerosol or short-range airborne transmission [30]. During the pandemic, the historic but still persistent concept of dichotomous separation between droplets and droplet nuclei using the 5-micron cut-off stood out as an important hurdle: although only particles smaller than 5 microns can reach the *alveoli*, this is of questionable relevance when considering that pathogens, such as SARS-CoV-2, can enter cells and also replicate in the upper tract of the respiratory system. In addition, it has been shown over the years that larger particles can remain suspended in air for varying lengths of time in a cloud of turbulent gas travelling well over the 1-to-2-meter limit which public health institutions initially adopted and that smaller droplets can rapidly evaporate in midair [31], effectively becoming *droplet nuclei*. There may have been a practical advantage in dividing the transmission routes of respiratory infections into droplets or aerosols using the 5-micron/1-meter cut-offs for public health considerations.

Nonetheless, many experts in the field have expressed criticism and concern about the rigid categorisation of particles, and several studies have shown the spread of the disease over wider distances. Some authors suggested that the reduced R0 base reproduction number of SARS-CoV-2 could be used as an indicative parameter of transmission by droplet and not aerosol [32]: although the mode of transmission is one of the components that contributes to the successful spread of a specific pathogen, there are many other factors to consider, including pathogenic mechanism, cell entry, and infectious dose. For example, if one were to compare *pertussis* and *tuberculosis* on the basis of R0 alone, one might think that the former is airborne and the latter by droplets. In fact, the only true "typical airborne pathogen" evidence that is missing for SARS-CoV-2 is the so-called long-range transmission. However, this does not rule out short-range aerosol transmission, especially in specific circumstances such as crowded and inadequately ventilated spaces. Indeed, mechanistic models have suggested that in close proximity to an infected person, the risk of exposure is greater for the short-range airborne route than for the classic droplet route [33]. Thus, airborne transmission has been progressively recognised as a significant mode of transmission of SARS-CoV-2, particularly considering these types of settings.

6. Protective Equipment

From a worker protection perspective, this acquired knowledge is diriment in defining which protective equipment is needed to warrant the protection of workers. One of the main preventive and protective measures taken during the COVID-19 pandemic has been using respiratory protective equipment. Several types of masks are available (N95/FFP2 respirators, surgical masks, and cloth masks), varying in filtering effectiveness, fluid resistance, and wearability. The scientific community of Occupational Physicians in Italy has contributed to their comparative analysis through numerous studies [34-38]. More recently, an important update on the topic has been published on the specific aspect of concern to the field of Occupational Medicine, aggregating, for the first time, evidence obtained from RCTs to compare the protective efficacy in the healthcare setting between filtering facepieces and surgical masks [39]. Previous updates had not identified RCT studies on face masks and SARS-CoV-2 infection in healthcare settings. In this study, surgical masks were found to be non-inferior to N95 concerning the risk of PCR-confirmed SARS-CoV-2 infection based on a prespecified noninferiority margin up to a doubling of risk. This update undoubtedly represents the synthesis of the highest quality evidence on the specific topic of the protective efficacy of different types of respiratory protective equipment.

Nonetheless, it is essential to note that, in more than three years since the beginning of the pandemic, and in consideration of the fact that healthcare personnel were the only occupational category adequately studied, only one randomised clinical trial and four observational studies have been able to provide evidence considered to be of sufficient quality. The classical approach of Evidence-Based Medicine (EBM) has demonstrated many limitations in the practical and timely application of evidence-based policies over time, as could be witnessed during the pandemic [40]. A heated scientific debate has opened within medical epistemology on whether the scientific method should be adapted to the new awareness of the complex systems present in reality, moving beyond the dogma of the hierarchy of probabilistic, clinical and epidemiological medical evidence, with systematic reviews/meta-analyses of randomised clinical trials at the top and case studies at the base, towards the inclusion of mechanistic evidence that studies and analyses the causal mechanisms of events. This new integrated, multi-disciplinary approach, called EBM+, involves the recognition and inclusion in biomedical research of evidence derived from *in vitro* experiments, biomedical imaging, animal experiments, aerosol science, engineering research, and simulations selected based on the specific questions. According to this new paradigm, vaccine efficacy of a new preparation is answered with the classical biomedical model involving the randomised clinical trial; otherwise, interventions that generate outcomes in complex systems require a new paradigm with designs that can capture dynamic changes, accommodate nonlinearity, and accept uncertainty: studying the efficacy of an instrument designed and produced with an engineering approach, whose efficacy can be for measured directly, needs the integration of mechanistic evidence. The mechanisms of respirator function are established and well understood. Certification systems, standards and occupational protocols for respirators are robust and minimise exposure to occupational hazards for millions of workers worldwide. For this reason, an RCT comparing respirators with devices of lower filtering efficacy, such as surgical masks, would not be reasonable to "prove" the value of protecting against chemical hazards. Similar paradoxes could not be considered for seat belts, parachutes or umbrellas. In application of this integrated approach, the IPC Working Group of the Italian National Institute of Health updated the technical note providing recommendations for the appropriate use of personal protective equipment against SARS-CoV-2 infection in healthcare and social care, indicating the use of respirators for all healthcare providers, based on the risk assessment of specific job/task/individual [41].

Finally, as a fundamental control applied at the receptor level, the vital role of vaccinations in reducing SARS-CoV-2 infections and COVID-19 worldwide should be underscored: up-to-date evidence demonstrate that COVID-19 vaccine-induced immunity and hybrid immunity provided by vaccinations and the natural infection offer the highest degree of protection to the individual workers [42, 43]. This impressive result was obtained thanks to the rapid clinical development and on-field availability of new pandemic vaccines based on mRNA and viral vector-based technology, reaching very high vaccination coverage among the target population during the first semester of 2021 in developed countries. It is worth highlighting the important role played by Occupational Physicians to jump-start the national vaccination campaign in workplaces, closely collaborating with Public Health Authorities and employers for the first time in Italy. This activity contributed to protecting individual workers exposed to the pandemic agent in different occupational settings, particularly the healthcare sector, and reduced its transmission within the broader community.

As an example of the impressive achievement obtained in the occupational setting, the most recent vaccine coverage data registered among healthcare workers in the European region, updated to November 2023, indicates that 90.4% were administered with the primary vaccination course and two thirds (67.0%) with the first booster dose [44]. However, only a minority (11.9%) reported a second booster dose, which should remind us not to lower the guard and continue being vigilant for possible new incident cases in the workplace.

7. Conclusions

Learning from these lessons, the Occupational Physician should rethink his role in the workplace, expanding his contribution from the minimum required by law, which often reduces the profession to bureaucratic functions, but instead draw on his expertise and specific competencies, acting as the go-to consultant in all matters of occupational health [45], to maintain and promote workers' health and wellbeing, as well as their work capacity. Additionally, it must be stressed that effective prevention of risk factors for workers' health further requires a multidisciplinary and integrated approach (i.e., between technologists and occupational physicians) during all phases and the decision-making process implicated in work [46]. In this endeavour to provide sound scientific reasoning in all his activities, particularly in the identification of occupational disorders caused by biological hazards, the Occupational Physician should remember, as crystallised in Bradford Hill's nine Points of View [47], that no single piece of evidence is sufficient, but that the different types of evidence should be combined to support the case for causation, as real-world circumstances often differ from those presented in scientific studies. Only through evidence-based practice approaches for assessing and characterising biological risk will improve, as data emerge and enhance our understanding of exposure and risk management, potentially in all occupational settings.

Declaration of Interest: Paolo Durando declares he was a member of the Working Group on Infection Prevention and Control established at the Italian National Institute of Health (ISS). The other Authors declare no conflict of interest.

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Cross-Sectional Study of the Psychological Well-Being of Healthcare Workers in a Large European University Hospital after the COVID-19 Initial Wave

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Key words: Health Care Workers; Psychological Support; COVID-19; DASS-21; PSS, IES-R; Anxiety; Depression; Stress-related Disorders

Abstract

Background: *The SARS-CoV-2 pandemic greatly impacted healthcare workers (HCWs) dedicated to COVID-19 patients. A cross-sectional investigation was conducted in a large European hospital to study the psychological distress of HCWs engaged in COVID-19 wards in the early phase of the pandemic.* **Methods:** *A questionnaire was sent to 1229 HCWs to collect the following information: i) sociodemographic data; ii) depression, anxiety, and stress scales (DASS-21); iii) event impact scale (IES-R); iv) perceived stress scale (PSS); and v) work interface analysis. Regardless of the outcome of the questionnaire, all subjects were offered psychological support voluntarily.* **Results:** *Approximately two-thirds of the workers reported no symptoms according to the DASS-21 scales, the corresponding figures for the IES-R and PSS scales being 36% and 43%, respectively. There were no differences in the levels of depression investigated through the different scales in the various occupational categories. Symptoms of anxiety, stress, and depression were more pronounced in women, whereas the highest stress levels were observed in the younger age groups. The highest scores were observed on the DAS-21 scales of anxiety and IES-R but not on the others. Only 51 workers, most with previous SARS-CoV-2 infection, sought clinical psychological counseling, and more than half received subsequent psychological support. Conclusions. Our results agree with most of the literature data that anxiety, depression, and stress are associated with gender (female), age (18-44 vs. over 55), and having cared for patients with COVID-19.*

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1. Introduction

The COVID-19 pandemic has been a traumatic event apart from the clinical consequences of infection on the psycho-emotional level of the general population and of specific categories professionally engaged in caring for SARS-CoV-2 patients.

Numerous studies have investigated the effects of the pandemic on the psychological condition of the general population [1, 2, 3] and on HCWs [4, 5, 6, 7]. According to a systematic literature review published through April 2020, anxiety was evaluated in 12 studies, with an overall prevalence of 23-2%, and depression was evaluated in 10 studies, with a prevalence rate of 22-8%. Female gender and nurses have higher rates of symptoms than males and medical staff, respectively. Insomnia prevalence was estimated at 38.9% across 5 studies [6].

In another systematic review in women and nurses, more frequent levels of moderate and severe levels of stress, anxiety, depression, sleep disturbance, and burnout were described. No significant age-related differences were observed. [8]. In a multicenter study conducted during the first pandemic wave on 906 employees from 6 hospitals by questionnaire collecting the prevalence of symptoms in the past month, the Depression Anxiety Stress Scales (DASS-21) [9] and the Impact of Events Scale-Revised (IES-R) [10] instrument, anxiety was detected in 5.3% of subjects, moderate to very severe depression in 8.7%, and moderate to extremely severe stress in 2.2% [11].

In another review, severe symptoms of stress, depression, and anxiety were recorded in 2.2%-14.5% of subjects with higher intensity with age, gender, occupational specialty, and frontline care of COVID-19 patients. The following mediating variables have been described: staff selection, preventive interventions, resilience, and social support [12].

The main factors described in the literature that contribute to increased physical and mental fatigue, anxiety, stress, and burnout of HCWs are limited hospital resources, fear of infection at work, longer shifts, son rhythms, work-life balance, consequent heightened dilemmas regarding patients' duties versus fear of family members' exposure, neglect of personal and family needs with increased workload, and lack of sufficient communication and up-to-date information [7].

Our work was carried out on workers of a socio-health territorial company in the Lombardy Region of Italy to assess the conditions of psychological distress experienced during the first SARS-CoV-2 pandemic phase.

2. Methods

This cross-sectional study was conducted in the period May-September 2020 at the *ASST Spedali Civili* of Brescia, one of the largest university hospitals in Italy, employing more than 8,000 workers and admitting more than 2000 COVID-19 patients in the period 15/02/2020-31/05/2020. The inclusion criterion to participate in the study was working in COVID-19 wards. The starting sample included 2,500 workers employed in both hospital and territorial services dedicated to the care of patients affected by SARS-CoV-2, including physicians, nurses, obstetricians, support workers, psychologists, office workers, and other health professionals (biologists, functional rehabilitation technicians, laboratory technicians, radiologists, etc.). Workers were recruited by e-mail, including a questionnaire that investigated the following areas: i) Sociodemographic data; ii) Depression, Anxiety, and Stress scale (DASS- 21) [9]; iii) Impact of event scale-revised (IES-R) [10]; iv) Perceived Stress Scale (PSS) [13, 14]; v) Work interface. The e-mails were sent to every worker in May, and further monthly e-mails were sent as recalls in June, July, and August to non-responders. Each enrolled worker gave his informed consent, compiled the questionnaire, and could express his interest, if any, in receiving counseling and psychological support from hospital psychologists and psychotherapists. The study adhered to the Ethical Principles of the Helsinki Declaration. In contrast, approval by the local Ethics Committee was unnecessary, as the study was performed as a health promotion activity in the context of mandatory Occupational Health Surveillance. The survey included the following validated self-administered questionnaires. For each scale, workers were asked to refer replies to the first wave of the COVID-19 emergency.

Depression Anxiety Stress Scales 21 (DASS-21) [9] is a 21-item self-report questionnaire that measures depression, anxiety, and stress symptoms, with seven items for each subscale. The scale is divided into five severity levels of depression, anxiety, and stress: normal, mild, moderately severe, and extremely severe. The cutoffs are different for anxiety, stress, and depression. The depression scale assesses devaluation of life, self-evaluation, hopelessness, lack of interest/involvement, dysphoria, inertia, and anhedonia; the anxiety scale assesses autonomic arousal, situational anxiety, musculoskeletal effects and subjective experience of anxious affect; and the stress scale assesses tension and irritability. Each item can have scores ranging from 0 to 3, while the sum for each subscale can vary from 0 to 21, with higher scores indicating higher levels of depression/anxiety/stress. For the depression subscale, none ranges from 0 to 9, mild 10 to 13, moderate 14 to 20, severe 20 to 27, and extremely severe > 28; for anxiety, none 0 to 7, mild 8 to 9, moderate 10 to 14, severe 15 to 19, extremely severe > 20; for stress, none is 0 to 14, mild 15 to 18, moderate 19 to 25, severe 26 to 33, extremely severe > 34.

The Impact of Event Scale-Revised (IES-R) [10] is a 22-item self-report questionnaire that studies the psychological impact of a stressful event. The IES-R comprises three subscales assessing intrusion (8 items), avoidance (8 items), and hyperarousal (6 items) symptoms. For this survey, participants had to refer to the COVID-19 emergency. IES-R items range from 0 to 4 (0 - not at all, 1 - a little bit, 2 - moderately, 3 - quite a bit, 4 - extremely), with a total score ranging from 0 to 88. Higher scores indicate higher subjective distress symptoms. For the IES-R scale, if the subject indicates scores of 0, 1, and 2 in any item, the impact of the events has no clinical value (score 0). On the other hand, if the subject indicates scores of 3 or 4 in fewer than three avoidance items, in no intrusiveness items, and in fewer than two hyperarousal items, the impact of events has subclinical value (score 1). When the subject indicates scores of 3 or 4 in some items in one of the three clusters and the other two have subclinical value or indicate scores of 3 or 4 in two of the three clusters, the impact of events has clinical value (score 2).

Perceived Stress Scale (PSS): [13] is a 10-item self-report questionnaire designed to measure the subjective perception of stress. It measures the degree to which life situations are appraised as stressful, asking about feelings and thoughts during the last month. PSS items range from 0 to 4, with a total score ranging from 0 to 40. Higher scores indicated higher subjective perception of stress. The sum of the scores for each item leads to the calculation of 3 stress levels: none (0-13 score 1), mild stress (14-26, score 2), and stress overload (27-40, score 3).

Workers were also asked to respond to specific items related to content data and work context, listed in Table 5, to which they attributed greater feelings of subjective discomfort.

Data collected via Google® forms were imported into Microsoft-Excel® and then into IBM-SPSS® software ver. 26.0.1. The normality of continuous variables was evaluated by the Kolmogorov–Smirnov test. After descriptive variable analyses, we performed χ^2 and Fisher's exact test analyses. Associations between variables in more than 2x2 tables were evaluated by the standard residual method, considering residuals as significant if higher than 1.96 in absolute value (z in the normal distribution). Spearman's correlation analysis was run to verify relationships among scores obtained at the different scales.

Nominal regressions were then performed, always setting as dependent variables Y (outcome) the psychological scale scores and as independent variables (predictors) gender, age groups, occupational category, taking care of COVID-19 patients, and previous COVID-19. Simple and multivariable models were run to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CI). All results were tested at the α significance level of 5%.

3. Results

A total of 1,229 workers completed the questionnaire and were enrolled in the study, with a response rate of 49,2%. The main characteristics of enrolled subjects are summarized in Table 1.

In both sexes, the age groups 30-44 and 45-54 years were more represented, with a significant prevalence of males in the first group and of females

Table 1. Distributions of main characteristics in the whole sample and after stratification by gender. Bold characters refer to figures significantly different between groups in the χ^2 test.

	Whole Sample		Males		Females	
Characteristics	**N**	**%**	**N**	**%**	**N**	**%**
Subjects	1,229	-	290	23.6	939	76.4
Age Groups*						
18-29 ys.	165	13.4	30	10.3	135	14.4
30-44 ys.	396	32.2	108	37.3	288	30.7
45-54 ys.	473	38.5	99	34.1	374	39.8
> 55 ys.s	195	15.9	53	18.3	142	15.1
Job Titles***						
Administrative Clerks	26	2.1	5	1.7	21	2.2
Support HCWs	248	20.2	37	12.7	211	22.5
Nurses	638	51.9	135	46.6	503	53.6
Physicians	241	19.6	98	33.8	143	15.2
Other Health Professions	76	6.2	15	5.2	61	6.5
Previously Affected by COVID-19						
No	966	78.6	220	75.9	746	79.4
Yes	263	21.4	70	24.1	193	20.6
Working in a COVID-19 Ward						
Yes	1,020	83	247	79.7	773	84.1
No	209	17	43	20.3	166	15.9

$^*p<0.05$; $^{***}p<0.0001$.

Table 2. Distribution of DASS-21 scale scores in the enrolled sample, stratified by sex. Bold characters indicate the subgroups showing significant differences in the χ^2 test analysis.

	DASS-21 Depression					DASS-21 Anxiety					DASS-21 Stress				
	M		F**		Both	M		F***		Both	M		F*		Both
Score	**N**	**%**	**N**	**%**	**%**	**N**	**%**	**N**	**%**	**%**	**N**	**%**	**N**	**%**	**%**
1. None	222	76.5	616	65.6	68.3	244	84.2	666	70.9	74.0	213	73.3	592	63.0	65.5
2. Slight	33	11.4	115	12.2	12.0	13	4.5	62	6.6	6.1	28	9.7	124	13.2	12.4
3. Moderate	22	7.6	131	14.0	12.4	25	8.6	121	12.9	11.9	24	8.3	120	12.8	11.7
4. Severe	7	2.4	35	3.7	3.4	1	0.3	39	4.2	3.3	17	5.9	78	8.3	7.7
5. Extremely Severe	6	2.1	42	4.5	3.9	7	2.4	51	5.4	4.7	8	2.8	25	2.7	2.7

$^*p<0.05$; $^{**}p<0.005$; $^{***}p<0.0001$.

in the second group. The distributions between genders were also significantly different for job titles ($p<0.0001$), as support HCWs prevailed among females, whereas physicians prevailed among males.

Table 2 presents the results of the DASS-21 scale in the whole sample as well as after stratification by sex. Females obtained significantly worse results in the three scales, especially in the anxiety scale ($p<0.0001$).

Table 3. Distributions of the IES-R and PSS scale in the enrolled sample, stratified by sex Bold characters, indicate subgroups showing significant differences (by gender) in the chi-square test analysis.

IES-R Scale, Score	Whole Sample		Males		Females***	
	N	%	N	%	N	%
0 (Impact of Events has No Clinical Value)	441	36	156	54	285	30
1 (Impact of Events has Subclinical Value)	584	47	108	37	476	51
2 (Impact of Events has Clinical Value)	204	17	26	9	178	19
PSS Scale, Score						
1 (No Stress)	528	43	170	59	358	38
2 (Mild Stress)	624	51	112	39	512	55
3 (Stress Overload)	77	6	8	2	69	7

$^{***}p<0.0001$.

The results of the IES-R and PSS scales are summarized in Table 3, again in the whole sample and after stratification by gender. Again, females showed the worst results on the IES-R, with a significant trend across the scale's severity levels (p<0.0001). In contrast, no significant difference was observed on the PSS scale according to sex.

Then, we verified the correlations among different scale scores, and the results are summarized in Table 4. The obtained scores were well correlated with each other in a highly significant manner (p<0.0001), with *rho* values ranging from 0.39 to 0.64.

Nominal 1 regression analyses investigating the associations between scale scores and individual variables were then performed calculating both crude (one-by-one analyses) and adjusted (multivariable analyses) ORs and 95% CI.

We obtained some significant associations, which are reported in Table 5, showing the importance of sex and age as main factors affecting the scores of different scales. Females and younger age groups showed significant associations with higher severity scores in the three DASS-21 domains, as well as in the IES-R and PSS scales. Assistance in COVID-19 wards showed a significant association with the DASS-21 anxiety and IES-R scales.

Table 4. Results of the Spearman's correlation analysis among the scores scale obtained with different scales.

	Das-21 Depression	Das-21 Anxiety	Das-21-Stress	IES
Das-21 Anxiety	0.58***			
Das-21 Stress	0.64***	0.58***		
IES-R	0.39***	0.42***	0.47***	
PSS	0.53***	0.46***	0.56***	0.43***

$^{***}p< 0.001$.

Regarding the opinion of workers about the main work content and context elements affecting their wellbeing, Table 6 shows the frequencies of answers in descending order. The main elements affecting psychological workers' health were the fear of contagion, organization of work, sense of helplessness in the face of patients' death and workload. In the subgroup of HCWs requiring psychological counseling, similar distributions were found, but higher relevance was observed for "relationships with organization".

Fifty-one (13 M, 38 F) HCWs required clinical psychological counseling. Twenty-two workers had only one psychological interview, and 29 were taken in for ongoing psychological support.

4. Discussion

The present study was performed at the end of the first COVID-19 pandemic phase in a large Italian hospital at the epicenter of the pandemic spread in Europe. In the early phase of the COVID-19 pandemic, digital resources such as online questionnaires published in the enterprise intranet allowed the Occupational Health Unit to manage hundreds of COVID-19 infections and contact tracing, thus overcoming the scarce resources available [15]. In

Table 5. Results of multinomial regressions. The results are expressed as odds ratios (ORs) and 95% Confidence Intervals (95% CI). Both crude (OR) and adjusted ORs (^{adj}OR) were calculated.

Score	Scales	OR	95% CI	^{adj}OR	95% CI
DASS-21 DEPRESSION					
1	*1 (Ref)*				
2	*No Association*				
3	Gender: F *vs* M	2.15**	1.33-3.46	2.06*	1.27-3.35
4	Age: 18-29 *vs* > 55 y	10.99*	1.37-88.06	10.54*	1.28-86.98
	Age: 45-54 *vs* > 55 y	8.54*	1.13-64.44	9.07*	1.19-69.21
5	Gender: F *vs* M	2.52*	1.06-6.02	3.01*	1.24-7.32
DASS-21 ANXIETY					
1	*1 (Ref)*				
2	*No Association*				
3	Gender: F *vs* M	1.77*	1.13-2.80	1.56	0.98-2.48
	Age: 18-29 *vs* > 55	2.48**	1.34-4.60	2.47*	1.29-4.74
4	Gender: F *vs* M	14.29*	1.95-104.56	13.23*	1.80-97.39
	COVID-19 Ward (Yes *vs* No)	8.45*	1.15-61.93	9.73*	1.28-73.85
5	Gender: F *vs* M	2.67*	1.20-5.96	2.47*	1.09-5.57
DASS-21 STRESS					
1	*1 (Ref)*				
2	Gender: F *vs* M	1.59*	1.03-2.47	1.63*	1.04-2.56
	Age:18-29 *vs*>55 y	2.72**	1.42-5.24	2.18*	1.10-4.33
	Age: 30-44 *vs*>55y	2.07*	1.14-3.73		
3	Gender: F *vs* M	1.80*	1.13-2.87	2.04**	1.26-3.30
4	Gender: F *vs* M	1.65	0.96-2.85	1.84*	1.05-3.22
5	Age: 18-29 *vs* > 55	4.22*	1.11-15.97	5.24*	1.29-21.29
IES-R					
0	*1 (Ref)*				
1	Gender: F *vs* M	2.41***	1.81-3.21	2.58***	1.91-3.47
2	Gender: F *vs* M	3.75***	2.38-5.91	3.92***	2.45-6.25
	Age: 45-54 *vs*>55y	2.24**	1.31-3.85	2.02*	1.16-3.52
	COVID-19 Ward (Yes *vs* No)	2.50**	1.48-4.22	2.84***	1.60-5.06
PSS					
1	*1 (Ref)*				
2	Gender: F *vs* M	2.17***	1.65-2.86	2.20***	1.66-2.93
	Age 18-29 *vs* > 55	1.64*	1.06-2.53	1.40	0.88-2.21
	Age 30-44 *vs* > 55	1.60*	1.13-2.28	1.50*	1.03-2.19
3	Gender: F *vs* M	4.10***	1.93-8.71	4.48***	2.08-9.65
	Age 18-29 *vs* > 55	3.04*	1.22-7.60	2.81*	1.07-7.35

Table 6. Distributions in descending order of items judged by workers as determinants of their psychological health.

	Whole Sample		Psychological Counseling	
Content and Context Items	**N**	**%**	**N**	**%**
Fear of Contagion	521	42	22	43
Organization of Work	444	36	20	39
Sense of Helplessness in Face of Death of Sick Person	444	36	19	37
Workload	439	36	18	35
Reconciliation of Work and Family	361	29	14	27
Change of Activity in Ward (Transformed into a COVID-19 Ward)	321	26	8	16
Fear of Not Caring Adequately	271	22	11	22
Shifts and/or Schedules	144	12	4	8
Relationship with Organization	143	12	13	25
Change of Department	98	8	1	2
Relationship with Colleagues	91	7	5	10
Other Issues	71	6	3	6
No Spect	20	2	1	2

that phase, the enterprise intranet was the main communication channel about preventive emergency measures to spread to HCWs, who gradually began to use it with increasing confidence.

Based on such premises and the limited available resources, eager to know the mental health status of our operators, we decided to perform the psychological survey again based on online questionnaires sent by e-mail to the target population. We knew such an approach was prone to several biases, including selection bias and uncertain data quality. Nevertheless, we believed this was the only way to approach such a relevant issue.

To better characterize the psychological impact of the pandemic on the psychological sphere, we decided to administer three different scales to investigate behavioral and emotional symptoms in our study group. The DASS-21 scale investigates the levels of depression, anxiety, and stress, whereas the IES-R scale investigates stress-related symptoms, and the PSS scale allows a rating of perceived stress.

The DASS-21 scale demonstrated slightly higher levels of stress and depression compared to anxiety, with figures of approximately 30% and 25%, respectively. The three symptoms significantly prevailed among females for depression and stress at a moderate level. In contrast, the prevalence was significant for anxiety in the medium to severe and extremely severe grades.

Regarding the IES-R scale, stress-related symptoms again prevailed significantly among females, particularly at level 2 (clinical significance), where the prevalence was more than double that of males. Similar results were observed with the PSS scale, where the last figure was approximately triple in females *vs* males. The scale scores were highly related, demonstrating good concordance.

In further nominal multivariate analyses, a higher susceptibility of females to symptoms recorded through the DASS-21 scale was confirmed, as well as a higher risk for younger (in particular the 18–29-year group) *vs* older subjects (older than 55 years). Delivering care in a COVID-19 ward was a further risk factor for anxiety symptoms. All such factors (female gender, 30-44 age group, and providing care in a COVID-19 ward) also played a role in stress-related symptoms revealed by the IES-R scale. In contrast, on the PSS scale, worse scores were associated with female sex and younger age.

Only 51 workers of the sample under analysis accepted the proposal of further clinical psychological counseling, 70% of whom had previously contracted COVID-19. Apart from this, the symptoms at the different scales were similar to the rest of the sample group (data not shown). Twenty-two received only psychological counseling, whereas 29 were in charge of further psychological support.

The main factors of the work environment affecting the workers' well-being resulted in decreasing order: fear of contagion, workload, organization, and sense of helplessness *vs* COVID-19 patients. The subset of HCWs who required psychological counseling judged the work similarly but showed the worst relationship with the organization.

This contribution, although with the limitations represented using self-administered questionnaires sent by e-mail and the cross-sectional study design, was conducted on a vast population of HCWs (1,229 workers). The impact of the pandemic led to the development of stress symptoms, anxiety, and depression of varying levels in approximately 30% of HCWs employed in the inpatient wards of COVID-19 patients, with stress symptoms of higher magnitude than anxiety and depression. The obtained results are consistent with literature data on the same topic, with recent reviews highlighting the role of age and gender as the main factors affecting the risk of developing symptoms of anxiety, depression, and stress. Most studies agree in showing a higher risk among females and as a function of age (higher in younger subjects) [6, 3, 12, 16, 17].

On the other hand, our results seem to disagree with some literature studies [6, 12, 16] that show a higher prevalence of psychological effects in nurses and support workers. Our research found no statistically significant association between psychological disorders and professional categories in multivariable analysis. Furthermore, in other studies [7,18], health workers attribute fatigue and stress to excessive workload and organization; however, in our research, they were more likely to fear infection.

Our sample showed little inclination to seek psychological support; only 51 workers agreed to psychological counseling, most of whom had previously contracted SARS-CoV-2 infection. We cannot exclude that such an event can have conditioned their option, as it is known that COVID-19 can leave clinical sequelae, including psychological symptoms [19, 20, 21]. We cannot exclude the possibility of missed workers undergoing psychological counseling or support on their own, outside our hospital, for privacy reasons. On the other hand, most HCWs did not seek psychological help during the entire emergency period, which may be explained by the challenging conditions in which they lived, personally and professionally.

The concordance between the DASS-21, IES-R, and PSS scales shows that they are valuable tools that can be used to study pandemic events. At the same time, the differences recorded in the description of the extent of symptoms can be explained by differences in the rationale and sensitivity of the different scales in recording the symptoms themselves.

We are aware that our study, performed by online questionnaires, was potentially affected by selection bias and inaccuracy due to a lack of control of data quality, potentially affecting the overall data quality and reliability. Nevertheless, the obtained data substantially agreed with comprehensive literature on the same topic, indirectly supporting an acceptable rate of collected data.

The study modified the questionnaire instructions by requiring participants to refer to events that occurred approximately three months earlier and not the previous week. This may have increased recall bias and affected the results.

5. Conclusion

Our study shows the presence of symptoms of stress, anxiety, and depression of varying levels in approximately one-third of HCWs employed in the care of COVID-19 patients, with symptoms influenced by factors such as age and gender, in agreement with previous literature studies. Mental health-informed accompanying interventions are needed to facilitate HCW coping [6, 12, 22].

Our results highlight the need for rapid interventions (psychological and organizational) to reduce psychological distress among HCWs, as just proposed in the literature [23]. Given the low propensity for psychological intake evidenced by HCWs, it is crucial to respect workers' wishes regarding the type, timing, and content of such interventions (e.g., individual psychological counseling with a therapist or a support group with other HCWs, organizational interventions at work with attention to shifts, rests or departmental changes, and incentives to take vacations).

The study was performed in the months immediately following the development of the COVID-19 pandemic; therefore, longitudinal follow-up studies will be necessary to evaluate the trend over time and the developmental trajectories of anxious, depressive, and stress-related symptoms in the HCW population, as well as to identify risk and protective factors in the long term.

Informed Consent Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study, as it was performed in the health surveillance of workers in the occupational context, which is compulsory according to the Italian Decree 81/2008. Patient consent was waived due to the reasons explained above. Data were treated according to the Italian Legislative Decree 196/2003 and the EU Regulation 2016/679.

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Conflicts of Interest: The authors declare no conflict of interest.

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Quantitative Assessment of Asbestos Fibers in Abdominal Organs: A Scoping Review

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Keywords: Asbestos Fibers; Electron Microscopy; Occupational Diseases; Chrysotile; Amphiboles; Stomach; Colorectum; Small Intestine; Spleen; Bladder; Kidney; Gallbladder; Liver; Pancreas; Intra-abdominal Lymph Nodes

Abstract

Background: *Quantification of asbestos fibers has been mainly performed in the lung but rarely in other organs. However, this may be relevant to understanding better translocation pathways and the oncogenic effects of asbestos on the human body. Electron microscopy is the best technology available to assess the type of fiber, dimensions, and distribution of asbestos fibers in different tissues and as a biomarker of cumulative dose.* **Objectives:** *This scoping review aims to summarize the findings of the studies in which asbestos fibers have been quantified by electron microscopy, occasionally associated with X-ray microanalysis, in normal and pathological tissue of ten abdominal organs.* **Methods:** *A scoping review has been performed by searching articles that quantified asbestos fibers in abdominal organs by electron microscopy (Scanning- SEM or Transmission-TEM).* **Results:** *The colon and rectum, kidney, bladder, and abdominal lymph nodes were the organs with at least ten samples available with quantification of asbestos fibers. Asbestos fibers were detected in all the abdominal organs considered: the highest value (152,32 million fibers per gram of dry tissue) was found in the colon and was identified using STEM with EDS.* **Conclusion:** *The studies included were heterogeneous in terms of exposure and cases, type of samples, as well as analytical techniques, therefore we cannot confirm a specific pattern of distribution in any organ, based on the low homogeneity of the exposure status. The colon is the organ in which the number of fibers is the highest, probably because of exposure arising from both internal distribution of inhaled fibers and ingestion. Additional studies of the number of asbestos fibers in abdominal organs should be made to achieve better representativity.*

1. Introduction

Diseases caused by asbestos fibers still represent a relevant issue not only for medical reasons, but also for the social, legal, financial, and political consequences they entail [1].

Mineral fibers have been studied for decades using techniques including optical microscopy,

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scanning electron microscopy and energy dispersive spectrometry [2], but, surely, the advantages of electron microscopy (higher resolving power and the possibility to gain information on the chemical composition and crystalline structure of the fibers) make this technique the most accurate to quantify asbestos fibers in human tissues [3]. Despite the correlation found between exposure to asbestos and pulmonary and non-pulmonary diseases [4-5], the quantification of the fibers has not been widely explored, not even in organs for which asbestos is considered a risk factor for cancer (with the notable exception of the lung).

In two previous review articles, we reported the concentration of asbestos fibers in peritoneal and pleural tissue. In peritoneal tissue [6], asbestos fibers were found in 58% of the 100 samples collected. In pleural tissue [7], asbestos fibers were detected in 111 samples (78%) and were below the detectable limit in 31 samples (22%). The concentration of asbestos fibers detected in the positive samples was distributed from as low as 0.01 million fibers per gram of dry tissue (mfgdt) up to 240 mfgdt. However, the minimum concentration of fibers overlaps in the three types of tissues (normal pleura, pleural plaque, mesothelioma) in terms of range of magnitude.

We explored the current literature on asbestos fibers detected with electron microscopy in pathological and normal abdominal tissue of ten organs: the stomach, colorectum, small intestine, spleen, bladder, kidney, gallbladder, liver, pancreas, and intra-abdominal lymph nodes.

2. Materials and Methods

As this was conceived as an exploratory endeavor, PRISMA extension for scoping reviews was followed to summarize the literature [8] and evaluate if a systematic review could eventually be performed. The literature search was performed on the following databases: PubMed, Embase, Scopus, Web of Science, Ovid, and Cochrane. The search strategy was conceived to detect papers in which the asbestos fibers in tissues were determined by electron microscopy, so the string used was: "(asbestos) AND (electron*) AND ((stomach) OR (colo*) OR (intestin*) OR (spleen) OR (renal OR kidney) OR (bladder) OR (liver OR hepatic) OR (gallbladder OR colangio*) OR (pancreas) OR (abdom* AND lymph*))" on 26 April 2023.

The inclusion criteria for this review were: i) articles written in any language, regardless of the publication date; ii) articles reporting a quantification of asbestos through electronic microscopy in subjects with defined or undefined asbestos exposure; iii) articles reporting a quantification of asbestos present in the following organs: stomach, colorectum, small intestine, spleen, bladder, kidney, gallbladder, liver, pancreas, and intra-abdominal lymph nodes. The exclusion criteria were: i) articles not reporting a quantitative measure of the number of asbestos fibers found or reporting a measure by techniques other than electron microscopy; ii) studies in animals.

We also decided that case reports would be included in this review and that the exposure pathway to asbestos would not represent an exclusion or inclusion criterion. The results have been presented, where appropriate, taking in consideration the subjects with an occupational exposure to asbestos and the ones with an environmental or unclear exposure.

Figure 1 illustrates the results of the literature search; 1,937 articles were identified: after removing duplicates, and not pertinent articles, 23 articles were checked in the full text. 12 studies that fit our inclusion criteria were identified (all were published between 1981 and 2021). The references of each relevant article were manually searched, yielding no more papers.

The studies included in this scoping review reported the number of asbestos fibers mainly for grams of wet tissue, so we transformed the value for wet tissue into dry tissue, multiplying by 10.

3. Results

The 12 studies included in this review comprised 204 cases with at least 325 samples analyzed. For

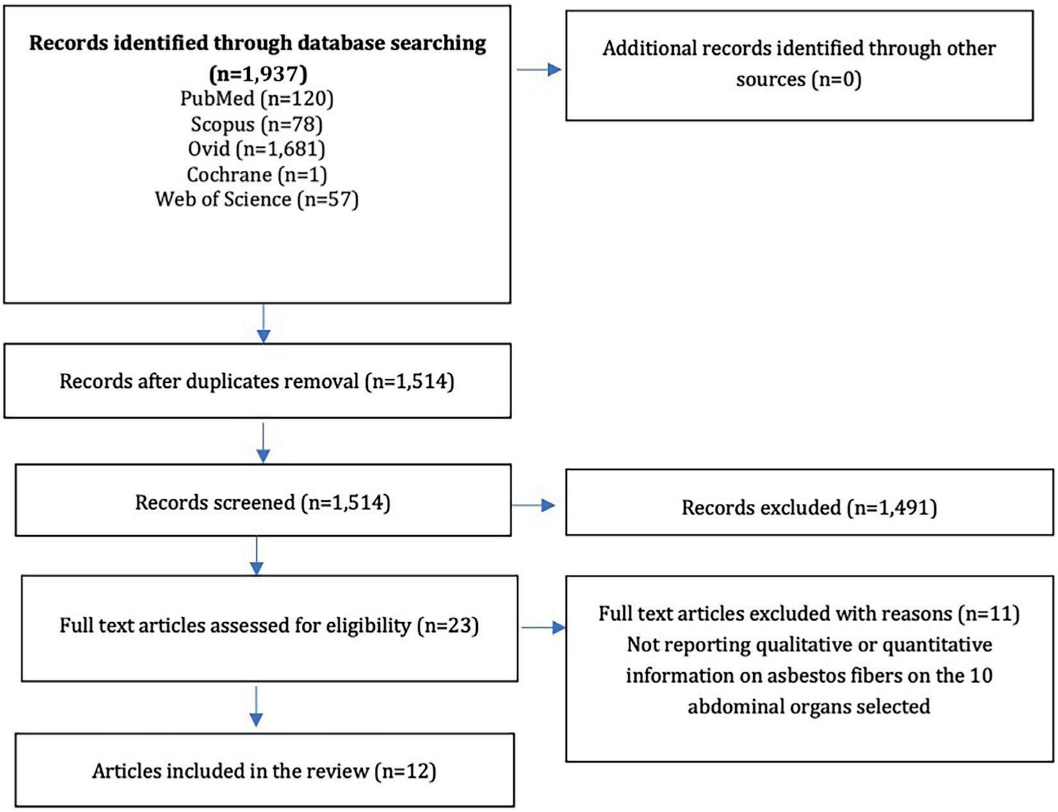

Figure 1. Flowchart showing the selection process of the articles included in the scoping review.

simplicity and better readability, we present the results divided by organs as follow:

- Table 1 reports a description of the patients and conditions included in the studies either normal or pathological tissue;
- Table 2 reports the detection limit (DL) of asbestos fibers in the intra-abdominal tissue (expressed as millions of fibers per gram of dry tissue: mfgdt) and the analytical technology used; when the detection limits was not specified in the study, we listed the lowest concentration of asbestos fibers reported.

The studies were performed on autopsy samples or biopsies. One study assessed stomach, small intestine, pancreas, spleen [9], five studies assessed large intestine [9, 10, 11, 12, 13], two assessed liver [9, 14], one assessed gallbladder [15], four studies assessed kidney (both cancerous and normal tissue) [9, 14, 16, 17], three studies assessed bladder [14, 18, 19], and one assessed abdominal lymph-nodes [20]. Seven of the studies found chrysotile [10, 13, 15, 16, 18, 20], seven found amphiboles [9, 10, 13, 14, 17, 19, 20], and two studies did not report which type of asbestos fibers were identified [11, 12]. The study with the highest number of samples was published by Ehrlich et al. [10], with 101 samples.

Out of the 204 cases, 72 (34.8%) were diagnosed with colon cancer, 25 (12.2%) with bladder cancer, 20 (9.8%) were controls with non-pathological colon, 5 (2.4%) with kidney cancer, 5 (2.4%) were controls with normal kidneys, 76 (37.2%) were either considered as other conditions or had pleural/lung cancer. In contrast, one (0.5%) was a "special-normal" kidney. This latter case was

Table 1. Number of cases and conditions found in the studies, grouped by the authors of the article.

Organ condition	N° of Cases or Samples	Reference Cronological Order
5 Normal Kidneys 5 Primary Adenocarcinomas of the Kidney 1 "Special-Normal Kidney"	9 Autopsies 2 Biopsies	Patel-Mandlik, 1981 [16]
1 Lung Cancer 2 Other Causes	3 Autopsies	Huang et al., 1988 [9]
40 Colon Cancers 20 Colon Controls	60 Biopsies	Ehrlich et al., 1991 [10]
12 Bladder Cancers	12 Biopsies	Molinini et al., 1992 [18]
1 Lung Cancer	1 Autopsy	Tossavainen et al., 1994 [17]
13 Bladder Cancers 12 Benign Prostatic Hypertrophies	25 Biopsies	Pollice et al., 1995 [19]
2 Asbestosis 1 Other Cause	3 Autopsies	Pollice et al., 1997 [14]
31 Colon Cancers 30 Other Causes	61 Cases	Muller et al., 2001 [12]
10 Lung Cancers 2 Asbestosis 2 Lung Fibrosis 8 Other Causes	22 Autopsies	Uibu et al., 2009 [20]
1 Malignant Pleural Mesothelioma	1 Autopsy	Croce et al., 2018 [15]
1 Colon Cancer	1 Biopsy	Rinaudo et al., 2021 [13]

categorized as "special-normal" because the subject had had kidney cancer on the contralateral kidney, which had been surgically removed.

3.1. Gastrointestinal Organs

3.1.1 Stomach

Only one study [9] reported asbestos fibers in the stomach. Overall, three patients were evaluated: two had been respectively surely or possibly occupationally exposed to asbestos, while the third one was not exposed. The samples were obtained during autopsies, and the analysis was conducted with TEM and EDXA technology.

The median of asbestos fibers detected was 2.62 mfgdt. Amphibole has been identified only in one sample, while the type of asbestos fibers found for the two other samples was not reported. Considering the three values, we can see a difference in asbestos fiber concentration between the exposed subjects (2.62 and 3.82 mfgdt) and those not exposed to asbestos during his working life (0.04 mfgdt).

3.1.2 Small Intestine

A quantification of fibers in small intestine tissue was done in one study [9]. Huang et al. [9] analyzed three small intestine samples (three cases) using TEM with EDXA. One case was not exposed to asbestos before, and no fibers were detected. Another case was occupationally exposed; the sample had a burden of 0.54 mfdgt (only amphiboles were found). The last case was occupationally exposed, and the sample had a burden of 1.24 mfdgt (mostly amphiboles).

3.1.3 Colon and Rectum

Studies which assessed colon and rectum content of asbestos are reported in Table 3. Five studies [9, 10, 11, 12, 13] analyzed the number of asbestos

Table 2. Detection limit of asbestos fiber's type and technology used.

Technology used	Chrysotile LOD*	Amphibole LOD*	Reference Cronological Order
TEM with SAED	**	**	Patel-Mandlik, 1981 [16]
TEM with EDX	0.04	0.04	Huang et al., 1988 [9]
STEM with EDS	0.076 (control group) 0.95 (exposed group)	0.076 (control group) 0.95 (exposed group)	Ehrlich et al., 1991 [10]
TEM with EDS	0.02	0.02	Molinini et al., 1992 [18]
SEM	0.1	0.1	Tossavainen et al., 1994 [17]
TEM with EDS	0.006	0.006	Pollice et al., 1995 [19]
TEM with EDS	0	0	Pollice et al., 1997 [14]
SEM with EDX	0.063	0.063	Muller et al., 2001 [12]
TEM with EDX	0.05	0.02	Uibu et al., 2009 [20]
SEM and EDS	3	3	Croce et al., 2018 [15]
SEM with EDS	0.03 (Healthy tissue) 0.08 (Neoplastic tissue)	0.03 (Healty tissue) 0.08 (Neoplastic tissue)	Rinaudo et al., 2021 [13]

***Limit of Detection (mfgdt):** *When the DL was not specified the lowest value observed was reported.*
*******The article reports, "If no fibers were observed in ten grid openings of two grids prepared from 100 mg dry weight of tissue, the value of F/mg dry weight would be Below Detection (BD) level."*
TEM= Transmission electron microscope, SAED= Selected area electron diffraction, EDX=Energy Dispersive X-ray Analysis.
EDS=Energy dispersive X-ray spectroscopy, SEM=Scanning electron microscope, ATEM=Analytical Transmission electron microscope.
STEM: Scanning Trasmission Electron Microscopy

fibers in the colorectal area. Overall, 210 samples were collected from 134 patients. The authors did not find asbestos fibers on 93 samples out of the total 210, representing 44.2% of the sample. Both normal tissues and cancerous tissues were analyzed. Most of the samples were collected from biopsies except for seven autopsies. The group includes subjects with known or probable occupational exposure (n=107) and subjects with unknown or impossible occupational exposure (n=27). The patients (n=61) included in the study from Muller et al., 2001 [12], were mixed (both occupational and unknown exposure). Amphiboles have been detected only in seven, and chrysotiles in eleven samples. The only amphiboles reported were amosite [10] and tremolite [13]. In the other cases, the type of asbestos fiber was not reported.

The range of asbestos fibers detected in the exposed subjects was 0.03-152.32 mfgdt; the range of fibers detected in unexposed or with unknown exposure subjects was 0.10-16 mfgdt. Only one study [10] did not find asbestos fibers in unexposed subjects.

In one study [9], the assessment was carried on using TEM and EDXA; in another study [10] STEM and EDS were used. In the 3 remaining articles, the sample evaluation was made using SEM and EDXA. [11-13]

In the study by Rinaudo et al. [13], three samples were digested and assessed to count the quantity of fibers, while three other samples were sliced, embedded in paraffin, and assessed for length and thickness. The range for length goes from 4.81 to 12.21 μm, while for thickness ranged from 0.98 to 2.1 μm.

3.1.4 Pancreas

An analysis of pancreatic tissue appears only in the study by Huang et al., 1988 [9]. The authors took a single sample from each of the three male subjects they had available and analyzed them using TEM and EDXA. Two of three pancreatic samples (66%) presented asbestos fibers, while one did not. As described in the article, case 1 had lung cancer with occupational exposure to asbestos and several

Table 3. Studies which assessed colon and rectum content of asbestos.

Value or range Range of Asbestos Fibers (mfgdt)	Type of Asbestos (N Samples With/ Without Fibers)	Asbestos Exposure	Type of Tissue Analyzed	N Subjects/ N Samples	Reference
*(0.10)	Total (1/0)	Unexposed	Colon	1/1	Huang, 1988 [9]
*(0.15)	Total (1/0)	Unexposed	Rectum	1/1	
*(0.47)	Total (1/0)	Occupational	Colon	1/1	
*(0.29)	Amphiboles (1/0)	Possible (occupational)	Colon	1/1	
*(0.88)	Total (1/0)	Occupational	Rectum	1/1	
*(0.20)	Amphiboles (1/0)	Possible (occupational)	Rectum	1/1	
ND	Total (0/40)	Unexposed	Colon (cancerous & normal mixed)	20/40	Ehrlich, 1991 [10]
*(11.29)	Amphiboles (1/39)	Occupational	Colon (cancerous)	40/40	
1.21-152.32	Chrysotile (9/31)				
1.85-5.86	Amphiboles (2/19)	Occupational	Colon (normal)	21/21	
ND	Total (0/1)	Unknown	Colon (normal)	1/1	Saitoh, 1993 [11] *
MD-0.000001	Total (2/1)	Unknown	Colon (normal)	3/3	
ND	Total (0/1)	Occupational	Colon (cancerous)	1/1	
0.06-0.35	Total (31/0)	Occupational/ unknown	Colon (cancerous tumor area)	31/31	Muller, 2001 [12]
0.06-0.21	Total (31/0)	Occupational/ unknown	Colon (cancerous non tumor area)	31/31	
0.06-0.21	Total (30/0)	Occupational/ unknown	Colon (normal)	30/30	
*(0.03)	Total (2/0)	Unknown	Colon (normal)	1/2	Rinaudo, 2021 [13]
*(0.08)	Total (1/0)	Unknown	Colon (cancerous)	1/n.a.	

** Only one value. Range not available*

asbestos fibers of 1.3 mfgdt, case 2 died from a cardiovascular accident with possibly occupational exposure, and the sample showed an asbestos amount of 0.45 mfgdt, case 3 died for other cause without asbestos exposure, and no fibers were found in the pancreatic tissue. Both amphiboles and chrysotiles were found with a higher concentration of the first type than the second type. Data about the length of fibers was available and described for case 1 and case 2. The case 3 had no information. Fiber size from case 1 had a mean length of 5.1 µm and a range from 2.1 to 16.0 µm. Case 2 had a mean length of 3.0 µm and a range from 1.6 to 7.8 µm. The ranges in fiber lengths varied widely in both lungs and other organs.

3.1.5 Liver

By analyzing three autopsies, Huang et al. [9] studied the association between asbestos fibers in human lung tissues and those in other extrapulmonary organs. Case 1 was occupationally exposed to asbestos for a prolonged period and suffered from asbestosis; occupational asbestos exposure in case 2 was possible but not certain, and no evidence of occupational asbestos exposure was found in case 3. The amount, type, and dimensions of asbestos fibers in the tissues of the liver and other organs were identified and measured by transmission electron microscopy (TEM). The detection limit for the liver tissue was 0.11 mfgdt. A concentration of 0.92 mfgdt was found in case 1, a concentration of 0.40 mfgdt was found in case 2, while in case 3, the fibers were not detectable.

Liver fiber type and length data were reported aggregated with pancreas and spleen data, so it is impossible to be more specific. The percentages of different types of asbestos fibers found by EDXA indicated that for case 1, 84.7% of fibers in the liver, spleen, and pancreas tissues were amosite; in case 2, 85.7% was anthophyllite. The mean fiber length in the liver, spleen, and pancreas was 5.1 µm in case 1 (range 2.1 µm -16.0 µm) and 3.0 µm in case 2 (range 1.6 µm -7.8 µm).

Pollice et al. [14] reported the concentration of asbestos fibers in 24 samples from 3 cases. The samples were extracted from different body organs, and only 1 was liver tissue sample analyzed with TEM and EDXA. The authors report that two subjects were affected by asbestosis with an occupational history of asbestos exposure. The case number 3 was a control with no occupational asbestos exposure reported. The analytical procedure described in the study does not specify the detection limit, but the minimum concentration detected was 0.1 mfgdt. Amphiboles were found in the liver tissue of one case (concentration: 0.15 mfgdt; mean length: 12µm, mean width 0.4µm), in the other case, and the control case, the authors found no fibers in liver tissue.

3.1.6 Gallbladder

The gallbladder tissue has been investigated only in one study [15], where the authors analyzed a section of the gallbladder from an 80-year-old woman who died of malignant pleural mesothelioma and was also affected by severe bile-tract problems (not specified). The exposure of this patient to asbestos was both environmental and occupational. Only chrysotile fibers were found in the sample analyzed with a concentration of 3 mfgdt. The techniques used for the detection of asbestos were SEM and EDS.

3.2. Urinary Tract

3.2.1 Kidney

Studies which assessed the content of asbestos fibers in the kidney are reported in Table 4. A quantitative assessment of asbestos fibers in kidney tissue was done in four studies [9, 14, 16, 17].

Huang et al. [9] analyzed three kidney samples (three cases) with TEM and EDXA. One of the cases had not been exposed to asbestos previously; the sample was free of asbestos fibers. Another case was possibly occupationally exposed; the sample had a burden of 0.47mfdgt (only amphiboles were found). The last case was occupationally exposed; the sample had a burden of 12.5mfdgt (mostly amphiboles). In the two cases in which asbestos was found, fibers were also assessed by length; in the possibly occupationally exposed case, the mean value for fibers' length was 3.1 µm, with a range of 2.2 to 4.3 µm. In the occupationally exposed case, the mean value for fibers' length was 5.1, with a range of 1 to 16 µm. No assessment was made concerning the width of the fibers.

Pollice et al. [14] analyzed three kidney samples (three cases) via TEM and EDS (Energy dispersive Spectrometry). One of the cases had not been exposed to asbestos previously; the sample was free of asbestos fibers. The other two cases were occupationally exposed; asbestos fibers were found in one of them (50%), which had a burden of 0.2 mfgdt. Only amphiboles were found, with a mean length of 18 µm and a mean diameter of 0.2 µm.

Patel-Mandlik et al. [16] analyzed two groups of people: one with kidney cancer and one without. Tissue samples were taken from medulla and/or cortex of both cancerous and normal kidney, or from a pool of medulla and cortex when it was not possible to define which part of the kidney had been sampled or when it had both portions. From the kidney cancer group, four samples of cortex and four of medulla were analyzed from three cases; another

Table 4. Studies which assessed the content of asbestos fibers in the kidney .

*Asbestos Fibers (mfgdt)**	*Type of Asbestos (N Samples With/ Without Fibers)*	*Asbestos Exposure*	*Type of Tissue Analyzed*	*N° of Subjects/ n° of Samples*	*Reference*
ND – 18.23	Chrysotile (1/3)	Unexposed	Cortex (normal kidney)	4/4	Patel-Mandlik, [16]
ND – 3.14	Chrysotile (2/2)	Unexposed	Medulla (normal kidney)	4/4	
Only one value (1.60)	Chrysotile (1/0)	Unexposed	Cortex and medulla pool (normal kidney)	1/1	
Only one value (24.55)	Chrysotile (1/0)	Unexposed	Cortex (cancerous kidney-tumor area)	1/1	
1.10–20.41	Chrysotile (3/0)	Unexposed	Cortex (cancerous kidney-non tumor area)	3/3	
0.74–86.91	Chrysotile (2/0)	Unexposed	Medulla (cancerous kidney-tumor area)	2/2	
1.27–47.92	Chrysotile (2/0)	Unexposed	Medulla (cancerous kidney-non tumor area)	2/2	
3.90–16.16	Chrysotile (2/0)	Unexposed	Cortex and medulla pool (cancerous kidney-tumor area)	2/2	
ND	Total (0/1)	Unexposed	Cortex and medulla pool (cancerous kidney-non tumor area)	1/1	
ND	Total (0/1)	Unexposed	Cortex (special-normal kidney)	1/1	
Only one value (17.63)	Chrysotile (1/0)	Unexposed	Medulla (special-normal kidney)	1/1	
ND	Total (0/1)	Occupational	Medulla (cancerous kidney-tumor area)	1/1	
ND	Total (0/1)	Occupational	Cortex and medulla pool (cancerous kidney-non tumor area)	1/1	
ND	Total (0/1)	Unexposed	Kidney	1/1	Huang [9]
Only one value (12.5)	Total (1/0)	Occupational	Kidney	1/1	
Only one value (0.47)	Amphiboles (1/0)	Possible (occupational)	Kidney	1/1	
Only one value (30)	Crocidolite (1/0)	Occupational	Kidney cortex	1/1	Tossavainen et al., [17]
ND-0.2	Amphiboles (1/1)	Occupational	Kidney	2/2	Pollice et al., [14]
ND	Total (0/1)	Unexposed	Kidney	1/1	

ND: Not detectable

sample of medulla tissue was taken from another case. Four other samples of pool of medulla and cortex were studied. From the normal kidney group, four samples of cortex and four of medulla were analyzed from four cases. Another sample of pool of medulla and cortex from another case was studied.

One last sample taken from a "normal-special" kidney was analyzed; it was categorized as "normal-special" because the case had a kidney cancer on the contralateral kidney, which had been surgically removed.

All samples were then analyzed with TEM and SAED (Selected area electron diffraction). In non-cancerous cortex, three samples were found free of asbestos fibers (75%); in the remaining sample 18.23 mfgdt were found. None of the cases were occupationally exposed. In non-cancerous medulla, two samples were found free of asbestos fibers (50%). The other two samples ranged from 2 to 3.1 mfgdt. The cases and samples were considered the same for non-cancerous cortex. For the non-cancerous medulla and cortex pool one sample was studied and it had asbestos fibers (1.6 mfgdt). The case was not occupationally exposed. In the cancerous cortex, 100% of the samples had asbestos fibers. The fibers ranged from 1.1 to 24.5 mfgdt. In cancerous medulla, one sample was found free of asbestos (20%), the other four samples ranged from 0.74 to 47.9 mfgdt. The only sample free of asbestos fibers was the only occupationally exposed case. In the group composed of cancerous pooled medulla and cortex two samples were free of asbestos (50%). The other two samples were from the same case, and they ranged from 3.9 to 16.1 mfgdt. Only one of the cases was occupationally exposed and it was free of asbestos fibers. Only chrysotile fibers were found in this study; there was not a significant difference in length and width of fibers between normal and cancerous kidneys. As stated in the article, the length of most fibers was between 0.4 to 0.6 μm, while the total range varied between 0.15 to 2.15 μm. The range of width was similarly very wide, with a minimum of 0.02 μm and a maximum of 0.15 μm in diameter.

Tossavainen et al. [17] analyzed via SEM (scanning electron microscopy) a single sample of kidney cortex from an occupationally exposed case with a diagnosis of lung carcinoma; the sample had a burden of 30 mfgdt. Only crocidolite fibers were found, with a length median value of 2.6 μm and a range that varies from 1 to 10 μm and a width median value of 0.12 μm and a range that varies from 0.05 μm to 0.21 μm.

3.2.2 Bladder

Studies that assessed the bladder content of asbestos are reported in Table 5. A quantitative assessment of asbestos fibers in bladder tissue was done in three studies [14, 18, 19].

Pollice et al. [14] analyzed three bladder samples using TEM and EDS (2 cases, occupationally exposed, and one control case, not exposed). The non-exposed worker was free of asbestos fibers in the bladder. Amongst the exposed workers, one of them (50%) was free of asbestos fibers in the bladder; the other one (50%) had a burden of 0.3 mfgdt. Only crocidolite was found, with a mean length of 3μm and a mean diameter of 0.05 μm.

Molinini et al. [18] analyzed 12 samples (12 cases of bladder cancer) via TEM and EDS. Eight of the cases had not been occupationally exposed to asbestos. Three out of 8 (37.5%) did not have any asbestos fibers; the other five cases (62.5%) had a burden of asbestos fibers that ranged from 0.075 to 0.58 mfgdt; in all cases only chrysotile fibers were found. The four remaining cases had been occupationally exposed to asbestos. In all of them (100%) asbestos fibers were found, ranging from 0.09 to 0.28 mfgdt; in all cases chrysotile fibers were found; in one of them, it was found along with tremolite. The dimension of asbestos fibers was assessed, with an overall mean length of 8 μm and a mean overall diameter of 0.16 μm. If only positive cases are taken into consideration, the mean length grows to 11 μm and mean diameter to 0.13 μm. Only in one case fibers longer than 40 μm were found.

Pollice et al. [19] analyzed 25 samples (13 cases of bladder cancer and 12 controls) using TEM and EDS. They divided exposure in five classes: class 1 (likely not exposed), class 2 (possible occupational exposure), class 2a (possible environmental exposure), class 3 (likely exposed), class 4 (occupationally exposed). Amongst the 13 cases of bladder cancer four belonged to class 1, six belonged to class 2, two belonged to class 3, and only one belonged to class 4. Eleven (84.6%) of them were free of asbestos fibers, the remaining two (15.4%) had a burden of 0.006 mfgdt (class 2, only chrysotile fibers were found), and 0.03 mfgdt (class 4, only crocidolite

Table 5. Studies that assessed the bladder content of asbestos.

Range of Asbestos Fibers (mfgdt)	Type of Asbestos Found (N Samples With / Without Fibers)	Asbestos Exposure	Type of Tissue Analyzed	N Subjects / N Samples	Reference
ND – 0.58	Chrysotile (5/3)	Unexposed	Bladder (cancerous)	8/8	Molinini et al., 1992 [18]
0.09– 0.28	Chrysotile (4/0)	Occupational	Bladder (cancerous)	4/4	
Only one value (0.26)	Total (1/3)				
ND	Total (0/4)	Unlikely	Bladder (cancerous)	4/4	Pollice et al., 1995 [19]
Only one value (0.006)	Chrysotile (1/5)	Possible	Bladder (cancerous)	6/6	
ND	Total (0/2)	Likely/ Occupational	Bladder (cancerous)	2/2	
Only one value (0.03)	Amphiboles (1/0)	Occupational	Bladder (cancerous)	1/1	
ND	Total (0/1)	Unexposed	Bladder	1/1	Pollice et al., 1997 [14]
ND-0.3	Amphiboles (1/1)	Occupational	Bladder	2/2	

fibers were found). Among the 12 controls, ten belonged to class 1, and two belonged to class 2. All of them were free of asbestos fibers. No dimensions of fibers were described in the article.

3.3. Lymphatic System

3.3.1 Spleen

Only one study reported the quantitative assessment of asbestos fibers in the spleen [9]. Overall, three patients were evaluated: two had been surely or possibly occupationally exposed to asbestos, while the third was not. The samples were taken during autopsies. The sample obtained by the unexposed patient did not show asbestos fibers, while the authors reported for the other two samples, respectively, 1.65 and 1.25 mfgdt. Amphibole has been identified in 1 sample, while the type of asbestos fibers analyzed for the other samples was not reported. The sample evaluation has been conducted with TEM and EDXA.

3.3.2 Intra-Abdominal Lymph Nodes

Studies assessing the asbestos content of intra-abdominal lymph nodes are reported in Table 6. Uibu et al. [20] analyzed by TEM with EDXA para-aortic and mesenteric lymph nodes and lung tissue from 17 subjects who underwent medico-legal autopsies for suspicion of asbestos-related disease and from 5 controls. It was shown that asbestos fibers could also translocate to the retroperitoneal and mesenteric lymph nodes besides their accumulation in lung tissue. Even low-level occupational exposure resulted in chrysotile or amphiboles in these abdominal lymph nodes. The mean concentration for the 10 subjects with a lung asbestos content of at least 1 mfgdt was 0.85 mfgdt in the para-aortic lymph nodes and 0.55 mfgdt in the mesenteric lymph nodes. The respective mean values for the 12 persons with a lung asbestos concentration of less than 1 mfgdt were 0.7 mfgdt for the para-aortic lymph nodes and 0.03 mfgdt for the mesenteric lymph nodes.

Table 6. Quantification of asbestos in the lymph nodes, grouped by fiber type and range and nature of exposure.

Asbestos Fibers (Mfgdt)*	Type of Asbestos Found (N Samples With/ Without Fibers)	Asbestos Exposure	Type of Tissue Analyzed	N Subjects / N Samples	Reference
ND - 4.36	Amphiboles (11/6)	Likely occupational	Para-aortic lymph node	17/17	Uibu et al., 2009 [20]
ND - 2.86	Amphiboles (10/7)	Likely occupational	Mesenteric lymph node	17/17	
ND	Amphiboles (0/4)	Unknown	Para-aortic lymph node	5/5	
ND	Chrysotile (0/1)				
ND	Total (0/1)				
ND	Amphiboles (0/3)	Unknown	Mesenteric lymph node	5/5	
ND	Chrysotile (0/1)				
Only one value (0.13)	Total (1/0)				

ND: Non Detectable

Table 7. Quantification of asbestos fibers in abdominal organs on studies with at least 10 samples available.

Range of Asbestos Fibers (Mfgdt) in Subjects With Unknown Exposure	Range of Asbestos Fibers (Mfgdt) in Unexposed Subjects	Range of Asbestos Fibers (Mfgdt) in Exposed (Or Possibly Exposed) Subjects	Organ
0.03–16	0.10–0.2	0.20–152.3	Colon and rectum
ND	0 – 86.9	0.2 – 30	Kidney
ND	0–0.6	0–0.3	Bladder
<0.05–0.13	Not detected	2.9–4.4	Abdominal lymph nodes

ND: Non Detectable

3.4. Number of Fibers in the Different Organs

Table 7 summarizes the results of the number of asbestos fibers in organs where at least 10 samples had been evaluated (colorectum, bladder, kidney, and intra-abdominal lymph nodes): the results are reported for 3 groups of subjects, categorized as exposed or possibly exposed, unexposed, or with unknown exposure.

The number of asbestos fibers in colorectal tissue is the highest among exposed (or possibly exposed) workers, with up to 152.32 mfgdt; additionally, it has the highest value for subjects with unknown exposure.

The kidney was the second organ with the highest number of fibers; however, it is remarkable to see that this organ's highest number of fibers (86.9 mfgdt) was detected in the unexposed group. The presence of any asbestos fibers was described in a study where the pooled relative risk of kidney cancer for asbestos exposure was 0.94 (95% confidence interval, 0.84-1.04), with no differences according to the type of asbestos fiber, geographic region, period of exposure, or estimated quality of the study [21]. No obvious differences can be observed for bladder tissue in the range of asbestos fibers in the three groups of subjects. Likewise, abdominal lymph nodes did not have any fibers detected in the unexposed group, which is remarkable and contrasts with the two other groups of subjects and organs analyzed.

3.5. Asbestos Fibers Dimensions

Seven articles [9, 13, 14, 16, 17, 18, 20] out of 12 studies reported data for the length and/or diameter of the asbestos fibers. Some articles reported the median, mean, or only the mode. For instance, Huang et al. [9] reported the overall dimension of the fibers as a whole and not divided by organ, hampering the possibility of predicting the distribution and/or any possible pattern of the fibers on diverse organs. Fibers' length was also assessed for the gastrointestinal tract in 2 cases; in the possibly occupationally exposed case, the mean value for fibers' length was 2.1 μm, with a range of 0.5-13 μm. In the occupationally exposed case, the mean value of fibers' length was 4 μm, with a range of 0.6 - 19 μm [9]. Another study reported the mode value of fibers' length (40 μm, with a range of 10-100 μm) and diameter (1.8 μm, with a range of 0,6-2.8 μm) in the colon samples analyzed [12].

3.6. Type of Fibers

Despite the large variability of studies described above, some conclusions can be drawn.

1. For the organs for which at least ten samples were available, the different range of asbestos fiber concentrations between exposed (or possibly exposed) subjects, non-exposed subjects, and subjects whose exposure was not clearly defined.
2. No significant differences have been observed in the detection limits in studies performed in different years, despite the technological advances in electron microscopy. Illustrative of that are Molinini's [18] and Uibu's [20] studies (published in 1992 and 2009 respectively): in both the detection limit using TEM microscopy was 0.02 mfgdt. An explanation for that is the improved sensitivity in today's technology: in past years differentiating between asbestos fibers and other types of fibers might have been difficult, therefore allowing for misclassification of the fibers themselves. Additionally, a critical factor in the detection of asbestos fibers in the sample is represented by the amount of tissue available.
3. For every organ, at least one article reported the presence of asbestos fibers, demonstrating a tropism for asbestos for all intra-abdominal organs. The translocation pathway of asbestos fibers and their tropism for some intra-abdominal organs might have a presumed role in carcinogenesis of some neoplasms [22]. In this study, both intraperitoneal and extra-peritoneal organs have been included.
4. The highest value for asbestos fiber concentration (152.32 mfgdt) was found in the colon by Ehrlich et al. [10] and it was identified using STEM with EDS. This also represents the highest value for chrysotile fiber concentration. The highest value for amphibole fiber concentration was also found in the colon by Ehrlich et al. and it was 11.92 mfgdt.
5. After analyzing all the articles found, we cannot highlight a distribution pattern in any organs. This cannot be generalized due to the low homogeneity of the exposure, and one must be prudent with the discussion of these results because the studies retrieved were performed on "convenience samples" This does not necessarily mean that those studies do not have a value: anyway, the information provided is not enough to draw firm conclusions about any possible pattern of distribution, but it is a good starting point.

4. Discussion

Currently, it is estimated that 125 million people are still environmentally exposed to asbestos worldwide, even in countries that banned its use [23]; however, no original articles have been published in the last five years regarding quantification of asbestos fibers in abdominal organs, being the latest study published on 2021 [13], except for a scoping review about quantification of fibers in the peritoneum published on 2022 [6].

It is well known that asbestos fibers enter the body through the respiratory system, from which they may be distributed to the whole body by the bloodstream or the lymphatic system. Asbestos fibers, mainly of the short type, have been found in all the abdominal organs included in this review: the stomach, colorectum, small intestine, spleen, bladder, kidney, gallbladder, liver, pancreas, and intra-abdominal lymph nodes.

The main contribution of this scoping review was to categorize ten abdominal organs to understand the presence of asbestos fibers and make an analytical assessment of the presence technology used and the dimension of the fibers found. The previous two scoping reviews [6,7] did not address the size of the fibers, so this is the first study that pays particular attention to the diameter and length of asbestos fibers.

It is known that the fibrogenicity and carcinogenicity of asbestos fibers depend on several fiber parameters including fiber dimensions [24].

It is important to emphasize that the quality of the findings does not exclusively depend on the microscope technology used but also on other factors such as the preparation of the samples (e.g., digestion procedure - strong acids/bases, plasma ashing, enzymatic digestion, etc.), the expertise of the laboratory personnel and the of the fiber's dimensions. In this regard, the amount of tissue analyzed is important: samples from autopsies generally have enough material, whereas this could not be the case for biopsies; thus, caution is required when comparing data from the two procedures.

Six studies included in this review used TEM and six used SEM. A comparison between SEM and TEM is a complex issue beyond this review's scope. The TEM vs SEM strengths are mainly the higher resolution, high magnification, and the possibility to get crystallographic information by SAED. At the same time, the main limitations are (i) the sample size (very small), (ii) complex sample preparation (quite critical), and (iii) limited surface detail and field depth. Field-emission SEM may allow us to obtain TEM-like magnification and resolution without the complexities of TEM.

A critical point in making sense of the data about the number of asbestos fibers present in each organ is not only the correct technique used for their determination but also that the sample should give a valid representation of the whole organ content. An additional issue is the clearance of asbestos fibers from the organ; this has been described, for example, for chrysotile fibers from the lung, but there are no studies regarding other human organs (most importantly, the pleura), although such studies exist in animals [25] and suggest that short fibers are more efficiently removed by mesothelium than long fibers. This adds to the critical importance of the issue of fibers' length.

One of the limitations of the current study is the significant variability among the articles. Since most of the samples analyzed have been convenient samples, it is possible to make the proper analysis to compare the studies, having only a non-probability sampling method.

The number of asbestos fibers in colorectal tissue is highest among exposed (or possibly exposed) workers, with up to 152.32 mfgdt. Additionally, it has the highest value for subjects with unknown exposure. We do not know the reason for this. Still, we speculate that all the population (including exposed and unexposed subjects) may introduce asbestos fibers through drinkable water, as during the last century, it has been a widespread practice in several countries to use cement-asbestos pipes to distribute potable water [26], and food. Thus, the colon (as the whole gut) would be subject to a double load of asbestos fibers: the fibers absorbed by the lungs and distributed through the bloodstream or the lymphatic circulation, and the fibers ingested with water and food. Drinkable water may contain asbestos fibers over millions per liter [27], and some foods may contain asbestos fibers over millions per gram [28]. In another study [29] that assessed asbestos fibers in extra-abdominal tissue it was found that the lymph nodes of occupationally exposed subjects has the highest value (7400 mfgdt).

In general, there is a prevalence of small fibers in the different organs included in this scoping review rather than longer fibers, which might be expected because longer fibers may have greater difficulty penetrating and traveling in the blood or lymphatic system.

To summarize, the studies included in this scoping review appear to be highly heterogeneous in terms of the study designs, the type of electron microscopy used for asbestos fibers assessment, and the exposure to asbestos in the selected cases as well, so one has to be cautious about the discussion of the type of fibers found, because the type of fibers in the samples would depend essentially on the kind of exposure. For example, if a subject has been exposed to chrysotile, the fibers found on the tissue would be chrysotile and not amphiboles.

Moreover, the fiber content of the different organs overlaps between exposed, possibly exposed, and unexposed subjects.

To reduce the inhomogeneity of the studies, we recommend that the quantification of asbestos fibers in human tissue should be made systematically on autopsies and biopsies when the technology and expertise are available, together with high-quality information about exposure to asbestos of the subject.

Further association of the quantification of the fibers in different organs shall be made with epidemiological studies with healthy or pathological tissues of abdominal organs so that the representativeness of the results about the general population may be more accurate.

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Occupational Risk Factors for Laryngeal Cancer in Tunisia: A Case Control Study

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Abstract

Background: *Tobacco use and alcohol consumption are the primary risk factors for laryngeal cancer (LC). In most populations, occupational exposures are likely to play a minor role in laryngeal carcinogenesis. We aimed to investigate the association between occupational exposure and laryngeal cancer.* **Methods:** *It is a case-control study that included 140 cases diagnosed between January 2013 and December 2016 and 140 controls matched by sex, age, alcohol consumption, and tobacco consumption.* **Results:** *Significantly increased risks were found amongst workers of the building sector (OR=4.621; 95% CI [1.826-11.693]) and the mechanical industry sector (OR=5.074; 95% CI [1.425-18.072]). Significant association of laryngeal cancer with various carcinogens was observed such as asbestos (p=0.009; OR=3.68; 95% CI [1.29-10.46]), paint vapors (p=0.005; OR=3.35; 95% CI [1.37-8.16]), solvents (p=0.001; OR=3.29: 95% CI [1.61-6.68]) and cement dust (p=0.003; OR=3.19: 95% CI [1.43-7.12]). After binary logistic regression, cement dust was independently correlated with LC (p=0.042; OR=3.93; 95% CI [1.04-14.78]. The administration sector was associated with decreased risk (p=0.001; OR=0.07; 95% CI [0.03-0.15]) as well as the health sector (p=0.001; OR=0.098; 95% CI [0.02-0.43]).* **Conclusions:** *Our results supported the role of occupational factors in developing LC. Further studies enabling an in-depth analysis of occupational exposures are necessary to provide a clearer definition of the etiological associations between single agents and circumstances of exposure and the genesis of LC.*

1. Introduction

Laryngeal cancer (LC) poses a significant public health challenge in Tunisia, ranking among the foremost cancers of the Ear-Nose-Throat (ENT) region [1]. The predominant histological form is squamous cell carcinoma, and it manifests with common symptoms such as hoarseness, dysphagia, odynophagia, neck mass, referred otalgia, and dyspnea [2]. Treatment options encompass surgery, radiation therapy, and chemotherapy, which can be employed individually or in combination [3].

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Understanding the full spectrum of lifestyle and environmental risk factors, especially occupational factors, is crucial for developing effective prevention strategies against this malignancy. While alcohol and tobacco are well-recognized as the primary risk factors for LC [4], a comprehensive work history and an inventory of associated products, coupled with vigilant monitoring of potentially exposed individuals, can aid in assessing the occupational contribution to this risk.

Asbestos (all forms) [5] and strong inorganic acid mists [6] have been identified by the International Agency for Research on Cancer (IARC) as two carcinogens potentially involved in the occurrence of LC (group 1) while hard bitumen emissions during mastic asphalt work and working in the rubber manufacturing industry [6] have been classified by IARC as agents with limited evidence in humans about carcinogenicity for the larynx.

Exploring the role of occupational and environmental factors in laryngeal cancer remains a relatively understudied area, particularly in middle and low-income countries. In this context, our study aimed to investigate the association between occupational exposure and LC in the context of the Tunisian population. Specifically, we focused on patients treated at the ENT department of the University Hospital Farhat Hached in Sousse, Tunisia.

2. Methods

It is a case-control study of occupational risk factors, which gained approval from the Ethics and Research Committee of the University Farhat Hached Hospital (IRB 00008931 as provided by OHRP). The study participants were recruited from a university hospital in Sousse, Tunisia. All patients diagnosed clinically with primary CL, confirmed by pathological examination, and followed either at the outpatient clinic and/or at the ENT department were eligible for inclusion as cases. Cases were recruited between 01 January 2013 and 31 December 2016. The inclusion criteria were professional activity (patients who were currently employed or who have worked previously) and agreement to answer the questionnaire were included in the study. Patients who passed away before the survey or who developed secondary laryngeal carcinoma were excluded. Cases were individually matched according to age, gender, tobacco consumption, and alcohol consumption to healthy participants with no history of cancer and selected randomly among the consultants of the Occupational Medicine department of the same hospital during the same period. At first, a random selection was made from the consultants' files. Matched controls were invited to participate in this survey and were informed that an investigator would shortly contact them. Exclusion criteria for controls were death or refusal of participation. All controls initially recruited were included in the survey.

Personal data and medical characteristics were filled out from the medical records in a standardized synoptic sheet. All participants were interviewed face-to-face by specially trained interviewers. Detailed occupational history was recorded by direct contact with the patient alone or with one of his relatives. The participants completed a questionnaire that included items related to occupational activity, performed tasks, number of years of work, use of carcinogenic products (cement dust, wood dust, asbestos...), analysis of possible exposure to the agents implicated in the literature in the development of LC, and a semi-quantitative estimation of this exposure. This estimate was made using the daily exposure frequency, work hours (H), years of exposure (D), and level of exposure (E). The level of exposure was rated, based on the nature of occupational activities and work environment, from 0 to 3, as follows: 0= minimally safe exposure; 1= indicates little product contact; 2= denotes moderate product contact; 3= contact with the product frequently.

An exposure index (I) for each product was calculated to approximate the cumulative exposure to that product: $I = H \times D \times E$. Tobacco consumption was quantified by "pack year" (PY), based on how many packs are smoked daily and for how many years. We defined a "current smoker" as a patient who has smoked at least 100 cigarettes in their lifetime and is currently smoking cigarettes. Alcohol consumption was assessed using the question: "Do you drink alcohol?". The main occupational exposures were defined according to the International Standard Classification of Occupations (ISCO 88) [7].

Univariate, multivariate, analytic, and descriptive statistical analyses were conducted. We used the chi-2 (χ^2) test and Student t-test in the univariate analysis. To identify the determinants of laryngeal cancer, we conducted a binary logistic regression method, and we included all variables with a p-value of less than or equal to 20% in the univariate analysis. The association was quantified using odds ratios (OR) presented with their 95% Confidence Intervals.

3. Results

During the study period, 252 patients were diagnosed with histologically confirmed laryngeal cancer. Many patients did not meet the inclusion criteria primarily due to being lost to follow-up or reported as deceased before the interview. The remaining cases included 140 patients who agreed to participate and were interviewed either directly during their hospitalization, during their consultation, or through their relatives.

We identified 140 LC cases meeting the inclusion criteria matched with controls. The mean age was 60.12±9.50 years, ranging from 39 to 82 years. There was a male predominance with a percentage of 95%, resulting in a sex ratio of 19. Alcohol consumption was reported by 31% of patients. The mean tobacco consumption was 46.4±18.4 PY, and 80% were current smokers. Notably, 28 patients (71.4%) had a family history of cancer, with the most common types being lung (71.4%), liver (14.3%), colon (7.2%), and brain (7.1%) cancers. Additionally, 21 patients (15%) had a family history of ENT cancer. The disease was detected incidentally in only one patient. The predominant symptom reported among cases was dysphonia, observed in 94.3% of cases. Dyspnea was the second most frequently noted symptom, occurring in 30% of cases, followed by dysphagia in 22.9%. Thus, glottic involvement was found in 116 patients (82.9%), supraglottic involvement in 100 patients (71.4%), and subglottic involvement in 62 patients (44.3%). Squamous cell carcinoma was the predominant histological type (97.1% of cases).

Verrucous carcinoma and sarcomatoid Carcinoma (1.45% each) were the other types reported. The majority of patients were manual workers (80.7%). The average seniority of workers in their last jobs was 17.28±10 years, with extremes of 2 and 45 years. An occupational seniority equal to or greater than 20 years was found in 37.9% of cases. A quarter of cases were working in the agricultural sector. Those working in the building sector and mechanical industry represented 17.1% and 10% of the cases (Figure 1). According to ISCO, the most represented occupational subgroup in our population were farmers and

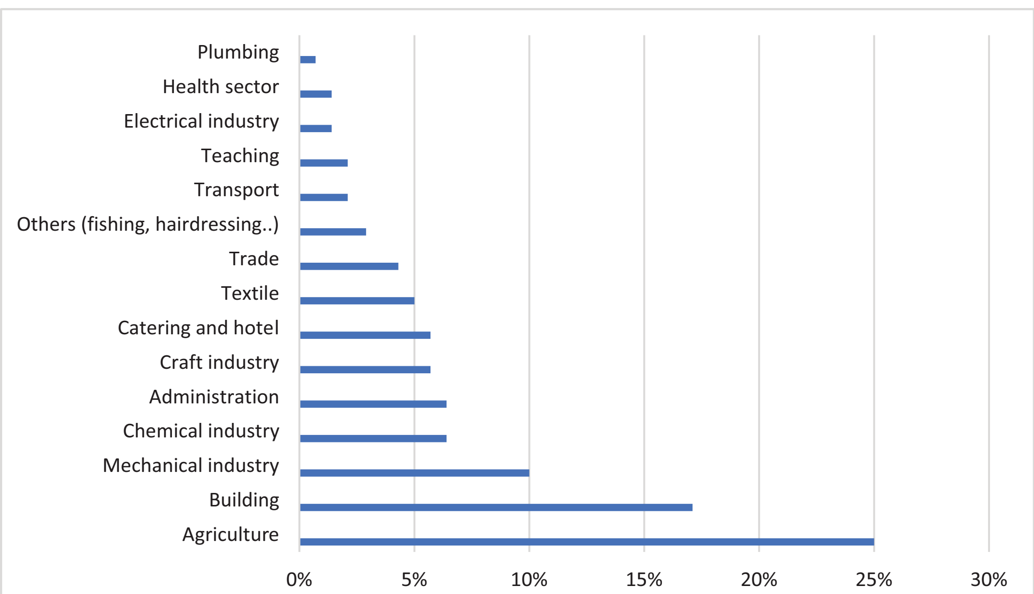

Figure 1. Distribution of patients according to their occupational sector.

Table 1. Distribution of patients according to the frequency of exposure to the considered agents and circumstances of exposure.

	Exposure		
Handled Products	Yes N (%)	No N (%)	Don't know N (%)
Cement Dust	25 (18)	114 (81.3)	1 (0,7)
Diesel Exhausts	15 (10.7)	125 (89.3)	0 (0)
Welding Smokes	13 (9.3)	127 (90.7)	0 (0)
Asbestos	15 (10.7)	109 (77.9)	16 (11.4)
Silica	18 (12.9)	117 (83.6)	5 (3.6)
Man-made Mineral Fiber (glass fibers, mineral wools)	18 (12.9)	107 (76.4)	15 (10.7)
Work in Plastic or Rubber Industry	7 (5)	132 (94.3)	1 (0.7)
Strong Inorganic Acid Mists	3 (2.1)	135 (96.4)	2 (1.4)
Cutting Fluids and Mineral OIL	9 (6.4)	127 (90.7)	4 (2.9)
Wood Dust	7 (5)	133 (95)	0 (0)
Textile Dust	8 (5.7)	132 (94.3)	0 (0)
Vapours from Solvents, Degreasers, and Diluents	33 (23.6)	107 (76.4)	0 (0)
Arsenic	6 (4.3)	117 (83.6)	17 (12.1)
Nickel	14 (10)	126 (90)	0 (0)
Chrome	13 (9.3)	125 (89.3)	2 (1.4)
Cadmium	5 (3.6)	125 (89.3)	10 (7.1)
Paint Vapours	21 (15)	119 (85)	0 (0)
Formaldehyde	3 (2.1)	129 (83.2)	8 (5.7)
Pesticide	27 (19.3)	113 (80.7)	0 (0)

skilled workers in commercial agriculture (21.4%), followed by skilled building workers (17.1%). Exposure to vapors from solvents, degreasers, and diluents was the most frequent and reported by 23.6% of patients. Pesticides were mentioned in 19.3% of cases, followed by cement dust in 18% (Table 1). The cumulative exposure was higher for pesticides, with a mean exposure index IE of 325.51±199.87.

According to the laryngeal tumor location, cancer was present in one anatomical region in 35% of cases. It invaded two and three regions in 31.4% and 33.6% of cases, respectively.

We studied the relationship between tumor size and frequency of exposure to risk products and there were no statistically significant differences between patients with one region location and those with more than one region location.

Table 2 summarizes the distribution of cases and controls according to their occupational category. Cases were significantly more frequently assigned to the construction, agriculture, trade, chemical industry, and textile sectors than controls. In contrast, controls were significantly more assigned to the administration, health, and direct services to individuals, protection, and security sectors.

The seniority of cases in their jobs was significantly more important in the administration, construction, agriculture, and health sectors (Table 2). An increased risk of LC was found for exposure to cement dust, asbestos, solvents, and paint vapors. As for the cumulative exposure, the exposure index to cement dust and asbestos was significantly higher in the cases than in the controls (Table 3).

After binary logistic regression, the only independent factor associated with LC was exposure to cement dust (OR=3.93; 95% CI [1.43-7.12]), whereas the area of administration was the only

Table 2. Distribution of cases and controls according to their occupational sector and seniority in their jobs.

		Cases	Controls	P	OR	95%CI
Administration	Frequency	9 (6.4)	68 (47.6)	**10^{-3}**	**0.07**	**[0.03-0-15]**
	Seniority	24.33±6.46	17.33±5.29	**10^{-3}**		
Building	Frequency	24 (17.1)	6 (42)	**10^{-3}**	**4.62**	**[1.82-11.69]**
	Seniority	19.66±7.82	17.5±0.7	0.20		
Agriculture	Frequency	32 (22.9%)	0 (0)	**10^{-3}**	-	-
	Seniority	24.9±9.59	-	-		
Transport	Frequency	6 (4.3)	4 (2.9)	0.520		
	Seniority	20.16±10.38	12.75±1.5	0.202		
Trade	Frequency	11 (7.9)	0 (0)	**10^{-3}**	-	-
	Seniority	16.27±5.96	-	-		
Chemical Industry	Frequency	5 (3.5)	1 (0.7)	0.214		
	Seniority	18.6±8.14	11	0.62		
Mechanical Industry	Frequency	14 (10)	3 (2.1)	**0.006**	**5.07**	**[1.42-18.72]**
	Seniority	16.28±6.24	12.33±2.521	0.68		
Textile	Frequency	7 (4.9)	0 (0)	**0.02**	-	-
	Seniority	18.85±5.33	-	-		
Craft Industry	Frequency	7 (4.9)	1 (0.7)	0.07		
	Seniority	20.85±9.51	12	0.417		
Health Sector	Frequency	2 (1.4)	18 (12.9)	**10^{-3}**	**0.09**	**[0.02-0.43]**
	Seniority	25±7.07	16.38±3.85	**0.011**		
Teaching	Frequency	3 (2.1)	5 (3.6)	0.473		
	Seniority	22.33±3.51	20.20±2.28	0.329		
Catering/Hotel	Frequency	6 (4.3)	3 (2.1)	0.498		
	Seniority	26.5±7.2	14±9.89	0.095		
Direct Service to Individuals/ Security	Frequency	7 (5)	22 (15.7)	**0.003**	**0.28**	**[0.11-0.68]**
	Seniority	15.85±4.29	15.8±6.02	0.98		
Electrical industry	Frequency	1 (0.7)	5(3.5)	0.214		
	Seniority	17	19.16±5.03	0.707		
Plumbing	Frequency	1 (0.7)	3 (2.1)	0.622		
	Seniority	17	16.66±5.8	0.96		
Others (Fishing, Hairdressing...)	Frequency	5 (3.6)	1 (0.7)	0.214		
	Seniority	25±9.4	19	0.59		

protective factor identified in our study (OR=0.15; 95% CI [0.06-0.38]).

4. Discussion

In our study, we identified several industries and chemicals associated with an increased risk of LC among Tunisian workers. However, this study has limitations. Given that this is a hospital-based case-control study rather than a population-based one, it could be susceptible to selection bias. However, it is noteworthy that the hospital where our patients were recruited is the biggest of the center of Tunisia and receives patients from urban and rural regions.

Table 3. Distribution of cases and controls according to the frequency of exposure to the considered agents and circumstances of exposure.

Risk Products		**Cases**	**Controls**	**P**	**OR**	**95%CI**
Cement Dust	Frequency	25 (18)	9 (6.4)	**0.003**	**3.19**	**[1.43-7.12]**
	IE	176.3±127.9	69.3±42.5	**0.012**		
Diesel Exhausts	Frequency	15 (10.7)	7 (5)	0.07	0.9	[0.6-.1]
	IE	116.0±82.2	92.6±65.3	0.51		
Welding Smokes	Frequency	13 (9.3)	6 (4.3)	0.09	0.8	[0.7-1.1]
	IE	123.1±95.3	105.3±48.0	0.67		
Asbestos	Frequency	15 (12.1)	5 (3.6)	**0.009**	**3.68**	**[1.29-10.46]**
	IE	161.1±99.3	36.0±72.0	**0.027**		
Silica	Frequency	18 (13.3)	9 (6.4)	0.05	0.9	[0.7-1.3]
	IE	163.1±135.0	68.0±57.6	0.11		
Man-Made Mineral Fiber	Frequency	19 (13.6)	0(0)	0.001	-	-
	IE	132.6±118.2	-	-		
Work in Plastic or Rubber Industry	Frequency	7 (5)	1 (0.7)	0.06	0.7	[0.5-0.9]
	IE	156.6±86.9	56	0.32		
Strong Inorganic Acid Mists	Frequency	3 (2.1)	2 (1.4)	0.68	1.0	[0.6-1.8]
	IE	168.0±207.5	140.0±5.6	0.86		
Cutting Fluids and Mineral OIL	Frequency	9 (6.6)	3 (2.1)	0.06	1.5	[1.2-2.1]
	IE	155.0±107.3	208±115.4	0.48		
Wood Dust	Frequency	8 (5.6)	3 (2.1)	0.12	0.7	[0.6-0.9]
	IE	133.9±114.8	68.0±57.6	0.19		
Textile Dust	Frequency	8 (5.7)	0 (0)	**0.007**	-	-
	IE	245.7±138.15	-	-		
Solvents, Degreasers, and Diluents	Frequency	33 (23.6)	12 (8.6)	**0.001**	**3.29**	**[1.61-6.68]**
	IE	178.4±134.8	154.7±51.4	0.76		
Arsenic	Frequency	6 (4.3)	1 (0.7)	0.12	0.8	[0.6-1]
	IE	256.0±163.0	152	0.58		
Nickel	Frequency	14 (10)	11 (7.9)	0.53	1.0	[0.7-1.6]
	IE	88.0±73.7	67.63±71.58	0.49		
Chrome	Frequency	13 (9.3)	7 (5)	0.16	1.4	[0.9-2.3]
	IE	84.3±.80.8	68.6±72.1	0.67		
Cadmium	Frequency	5 (3.6)	2 (1.4)	0.44	0.8	[0.5-1.1]
	IE	105.6±113.1	208.0±181.0	0.38		
Paint Vapours	Frequency	21 (15)	7 (5)	**0.005**	**3.35**	**[1.37-8.16]**
	IE	177.1±117.1	75.2±79.9	0.07		
Formaldehyde	Frequency	3 (2.1)	1 (0.7)	0.36	0.7	[0.7-1.0]
	IE	226.7±83.3	144	0.48		
Pesticide	Frequency	27 (19.3)	0 (0)	10^{-3}	-	-
	IE	336.3±200.93	-	-		

Population heterogeneity may influence the comprehension of posed queries. To address this bias, the questions asked were simplified, and each time, we ensured a genuine understanding of the question and its meaning. The assessment of occupational exposure was conducted in a semi-quantitative manner, which may not allow an objective consideration of exposure variability among different jobs.

It is often difficult to determine the fraction attributable to occupational exposure in the genesis of occupational cancers, mainly because of the multiple activities with variable workstations and exposures. Inhalation is the main entry route for many agents in the workplace, which makes the upper airway tract an anatomical region directly in contact with these nuisances. In France, the fraction of LC attributed to occupational exposure was 7.6% [8].

Most of our patients were blue-collar workers, either in their last job (80.7%) or in their previous job (77.3%). Through a literature review, LC was often associated with manual occupations. Indeed, according to a meta-analysis [9] combining the results of 21 case-control studies (6,906 cases and 10816 controls) with the same occupational exposures, there was a significant increase in the risk of LC for blue-collar workers (OR=1.3; 95% CI=[1.2-1.4]), whereas administrative and managerial staff and office and related workers had less frequent laryngeal cancer.

In our study, we found that most of the cases worked in the agriculture sector, building sector, and mechanical industry. In Turkey, the sector of textile and construction was mentioned as a risk sector of association with LC [10]. In Finland, working in the food industry increased this cancer risk by 30% [11].

4.1. Asbestos

In our study, asbestos exposure was found in 9.3% of cases in the current job and 12.5% in the preceding job, with a statistically significant increase in the risk of laryngeal cancer (OR=3.68; 95% CI=[1.29-10.46]). Laryngeal cancer and its association with asbestos exposure have been assessed in several studies. Indeed, Occupational risk factors for laryngeal cancer with a sufficient level of evidence include asbestos, which has been classified as a group 1 carcinogen for the larynx by the International Agency for Research on Cancer (IARC) since 2009 [5], as well as mists from strong inorganic acids, which have been classified as group 1 carcinogens since 2012 [6]. Two case-control studies were conducted in France [12] and Germany [13], showing that asbestos exposure increased the risk of LC, and this depended on the duration and intensity of exposure. A more recent French study focused on cases of work-related laryngeal cancers confirmed the role of asbestos in laryngeal carcinogenesis and showed that it was the laryngeal cancer risk factor most reported in the network from 2001 to 2016 [14].

4.2. Strong Mineral Acid Mists and Sulfuric Acid

Strong inorganic acid mists have been classified as a group 1 carcinogen with sufficient evidence for the larynx since 2012 [6]. Colin L. et al. reported that the effects related to sulfuric acid are increased by the duration of exposure and the degree of exposure [15]. Our study couldn't prove the relationship between exposure to acid mist and CL.

4.3. Cement Dust

Our study showed that exposure to cement dust had a significant association with an increased risk of LC (p=0.003; OR=3.19; 95% CI=[1.43-7.12]). In the multivariate study, this factor was independently associated with the occurrence of LC (pa=0.042; OR=3.93; 95% CI=[1.04-14.78]). Similarly, most of the studies conducted in many countries found a relationship between the risk of LC and exposure to cement dust [16, 17]. In a Swedish study, Purdue MP and coll. [18] observed a slight dose-response relationship depending on the intensity of exposure in construction workers exposed to cement dust.

Cement dust could pose a carcinogenic risk because it may contain hexavalent chromium, a known carcinogen [19], found in certain types of cement. Additionally, the lime content in cement, may potentially induce the production of reactive oxygen species [20]. However, exposures to asbestos, cement dust, and silica are strongly interconnected. Given the identification of an association between asbestos and LC in our data, it is difficult to investigate the individual impact of each exposure.

4.4. Wood Dust

According to IARC, wood dusts, which are carcinogenic to human (group 1), have an established role in the occurrence of cancers of the sino-nasal cavities [17]. The role of wood dusts in the occurrence of LC has been the subject of considerable research and speculation. In fact, our study did not show a statistically significant association (p=0.12). A meta-analysis done in 2012 showed a non-significant decreased risk of LC in wood workers (OR=0.95; 95% CI 0.80 to 1.14) [21]. On the other hand, in a cohort of workers exposed to softwood [22], the SIR (standardized incidence ratio) for larynx cancer was elevated (SIR 1.4, 95% CI 0.6 to 2.6).

4.5. Pesticides

Several pesticides are classified as potential (group 1) or probable (group 2) carcinogens by IARC. A recent case-control study [23] found a statistically significant association between pesticide exposure and LC after controlling for age, sex, and smoking (OR=9.33; 95% CI 1.65 to 52.68) with a dose-response pattern. In our study, the cases were more exposed to pesticides with a statistically significant difference but no association with LC was proven.

4.6. Man-made Mineral Fiber

Refractory ceramic fiber is classified as possible human carcinogens, whereas mineral wools are unclassifiable for humans [24]. In a meta-analysis of risks of cancers of the lung and head and neck from exposure to rock wool and glass wool, the summary RR for LC was 1.3 (95% CI 1.1 to 1.6) [25]. In a French cohort, the incidence of cancer was determined among workers employed in a French man-made mineral fiber production plant. It was significantly higher for the larynx (SIR 2.3) [26]. In our study, we were unable to assess the association between LC and exposure to these fibers because it was only observed among cases.

4.7. Work in the Rubber Industry

Work in the rubber industry is also classified as a Group 1 carcinogen by IARC but with limited evidence for human LC [5]. In a review to examine the epidemiological evidence on cancer risk among workers in the rubber industry, overall, the findings indicate the presence of a widespread moderate increased risk for LC [27]. In a meta-analysis, significantly increased meta-relative risk was obtained considering working in the rubber industry (meta-RR 1.39; 95% CI 1.13 to 1.71). However, working in the rubber industry involves complex and variable exposures, which depend on processing, work area, and period. The risk was increased for production workers, while the OR for tire makers and vulcanizers was equal to 1 [9]. A meta-analysis was conducted on observational studies published until April 2016 on work in the rubber industry and cancer risk. An increased risk was found for LC [standardized incidence ratio (SIR) [1.46; 95% CI 1.10 to 1.94] [28]. In our study, exposure to rubber was exclusively found among the cases. Consequently, we could not establish an association between the risk of exposure to these products and LC.

4.8. Silica

Known for its pulmonary carcinogenic effect, the role silica exposure in laryngeal cancer has been widely studied. A significantly increased risk of laryngeal cancer (OR=1.39, 95% CI 1.17 to .67) among workers exposed to silica dust was observed in a meta-analysis by combining six case-control studies with adjustment for smoking and alcohol consumption [29]. A hospital-based case-referent study was conducted to identify occupational risk factors for laryngeal cancer in Turkey [30]. A high risk was observed in workers potentially exposed to silica dust (OR=1.8; 95% CI 1.3 to 2.3). From our study, a role of silica dust exposure doesn't emerge.

4.9. Textile Dusts

Paget-Bailly et al. [9], reported a significant meta-RR of 1.4 for LC among textile workers. It was higher for textile work (meta-RR 3.20; 95% CI 1.72 to 5.98) than for textile dust exposure (Meta –RR 1.25; 95% CI 0.93 to 1.69). According to Elci OC et al. [30], specific exposure to cotton dust has an OR equal to 1.3 for exposed subjects with significant dose-response relationship. In a Finnish study, Kyyronen et al. [31] found an increased SIR with high cumulative exposure to textile dusts. Our results showed a statistically significant difference in textile dust exposure between cases and controls, with cases being significantly more exposed. However, no conclusive risk could be established because absence of textile dust exposure among the control group.

4.10. Solvents

Several authors have studied the association between exposure to organic solvents and LC, but the specific role of each type of solvent is poorly investigated. Our results have demonstrated that cases were significantly more exposed to solvents than the controls, with a statistically significant difference associated with a substantial increase in risk (p=0.001, OR=3.29; 95% CI=[1.619-6.683]). In a multicenter case-control study, Shangina et al. [32] found a significant increased risk associated with exposure to chlorinated solvents in men (OR=2.18; 95% CI 1.03 to 4.61). A case-control study conducted in France [33] observed a statistically significant association between cumulative exposure to Perchloroethylene (PCE) and LC (p=0.04). The OR was 3.86 (95% CI 1.30 to 11.48) for those exposed to the highest levels of PCE.

4.11. Welding Fumes

In 2017, welding fumes were recognized as a cause of lung cancer in humans [34]. In a Swedish case-control study, Gustavsson et al. [35], found an increased risk of LC in association with exposure for more than eight years to welding fumes (OR=2.0; 95% CI 1 to 3.7). In a meta-analysis of occupations and LC, Bayer et al. [36] found a meta-RR of 1.17 (95% CI 0.98 to 1.39) for welders and plumbers. From our study, a role of the exposure to welding fumes exposure doesn't emerge.

4.12. Diesel Exhausts

Paget-Bailly S et al. [9], from their meta-analysis on the risks of occupational cancers of the larynx have highlighted significant but moderate associations for exposure to engine exhaust and LC (Meta –RR 1.17; 95% CI 1.05 to 1.30]. No statistically significant association between diesel exhausts exposure and LC occurrence emerged from our study.

4.13 Metals

Many heavy metals seem to be involved in the development of several types of cancer. In our study, no significant association between exposure different types of metals has been proven. In a previous prospective study conducted in Sfax, Tunisia [37], there was a statistically significant association between the different metals and the incidence of LC and nasopharyngeal cancer. The ORs were 2.41 for arsenic; 4.95 for cadmium; 2.09 for chromium; 8.87 for nickel.

4.14. Formaldehyde

Formaldehyde is a proven human carcinogen by the IARC in relation to leukaemia and nasopharyngeal cancer [38]. For the laryngeal location, the results are less conclusive. Although some studies, found positive associations between occupational exposure to formaldehyde and LC [39], the meta-analysis carried out by Paget-Bailly et al. [9] did not support this hypothesis. In our study only three patients were exposed to this agent without a statistically significant association p=0.361.

5. Conclusions

Overall, several occupational risk factors have been incriminated in LC. In our study, the most incriminated chemical occupational substances were asbestos, cement dust, solvents, and paint vapors. The definite carcinogens were exposure to asbestos and strong inorganic acid mists. The rubber industry is the only work sector classified as a definite carcinogen by IARC for this cancer site. Otherwise, smoking and alcohol consumption are the most incriminated lifestyle factors, with a convincing level of evidence.

Preventing this cancer starts with fighting against these bad lifestyle habits and the intervention in the occupational factors. Further studies enabling an in-depth analysis of occupational exposures are necessary to provide a clearer definition of the etiological associations between single agents and circumstances of exposure and the genesis of LC.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Declaration of Interest: The Authors declare no conflict of interest.

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Workplace Bullying in Italy: A Systematic Review and Meta-Analysis

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Keywords: Workers; Bullying; Workplace; Organization; Health Status; Mental Health; Italy

Abstract

Background: *Within any work environment, employees may be affected by "workplace bullying", a form of violent and repeated social behavior towards subordinates and colleagues. This review aimed to investigate the prevalence of bullied workers in Italy, the causes of the phenomenon, and the consequences at physical, psychological, and organizational levels.* **Methods:** *We included observational studies and systematic reviews examining the prevalence of bullied workers and the causes and consequences in Italian workplaces. Data extraction and analysis were performed on all included studies. The research strategy included three electronic databases (PubMed, Scopus, and Web of Science). A comprehensive search was done to retrieve articles based on a PRISMA-compliant protocol registered in PROSPERO: CRD 42023394635.* **Results:** *One hundred eighty-four articles were retrieved, and once duplicates and irrelevant articles were removed, 42 useful articles were reviewed. The mean pooled prevalence, calculated based on workers complaining of mistreatment, was 6.7% (SD: 4,09) and increased significantly to 17.0% (SD: 12.88) when considering only healthcare workplaces. Causes include how impaired mental health and high workload reinforce the possibility of being bullied in the workplace, resulting in a worsening of the worker's quality of life (physical and psychological) and the work organization with increased absenteeism and job changes.* **Conclusions:** *Workplace bullying is a very present phenomenon within workplaces in Italy. In light of this, it is necessary to put prevention plans in place and find solutions to maintain optimal organizational well-being in the work environment.*

1. Introduction

According to the National Institute for Occupational Safety and Health (NIOSH), workplace violence is the act or threat of violence, ranging from verbal abuse to physical assaults directed toward persons at work or on duty [1].

Workplace violence can come from anyone and be directed at anyone; it can be subtle or overt, deliberate or unintended, and maybe a single event or involve a continuing series of incidents. In addition, violence can victimize both men and women and may be initiated by or directed toward workers, clients, and members of the public [2].

Workplace bullying is part of this phenomenon and represents a serious form of psychological harassment conducted systematically and continuously by colleagues or superiors against an employee to cause him/her harm and exclude him/her from the workplace. The purpose of bullying is to eliminate a person who has become inconvenient by inducing him/her to resign voluntarily or by causing a reasoned dismissal [3].

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It can be defined as "horizontal bullying" if it occurs between colleagues, "vertical bullying" if the victim is the employee or the employer, "corporate bullying" if it is the company that enacts this behavior against the employee, "strategic bullying" if it is carried out with well-defined strategies and "emotional bullying" if it is caused by negative feelings such as envy and jealousy [4].

Bullying may be direct or indirect aggression or a combination of both: direct bullying (physical and verbal) includes overt behaviors like hitting, threatening, and persistent humiliation in front of others; indirect bullying (non-verbal bullying) includes hidden behaviors. It is difficult to detect early and may include spreading rumors, withholding information, and intentionally isolating or excluding from a group [5].

Workplace bullying has negative effects on both the occupational well-being and the mental and physical well-being of workers. The most frequent disorders they suffer from are psychological disorders such as anxiety and depression, psychosomatic disorders such as headache, gastrointestinal and cardiovascular disorders, and behavioral disorders such as suicidal tendencies and alcohol and drug abuse [6]. The negative effects of bullying also affect work organizations with increased absenteeism due to illness [7] and the family with alterations in interpersonal relationships.

Data concerning the prevalence of workplace bullying worldwide are rather heterogeneous. There is wide variation in the reporting and recording of bullying worldwide. This may be due to several factors, such as lack of clarity in definition, variation in time frames assigned by the researcher, problems with validity and reliability of measurement, and organizational culture and structures [8].

In 2007, the Workplace Bullying Institute conducted the first representative study of adult Americans on workplace bullying. The study found that 37% of workers have been bullied [9].

According to the Fifth European Working Conditions Survey (EWCS: EUROFOUND, 2010), workplace bullying was estimated in 1.6% of the working population in the EU. However, this prevalence varied dramatically between countries, oscillating between 9.5% in France and 0.6% in Bulgaria. Since the method to estimate the prevalence of workplace bullying was the same across the countries that participated in the survey – that is, asking employees directly whether or not they considered they had been subjected to bullying over the past 12 months – it seems reasonable to think that personal and cultural factors might explain these vast differences [10].

Currently, in Italy, mobbing is not specifically recognized in the Civil or Criminal Code, though it conflicts with several regulations that sanction and regulate the proper conduct of work activities. The judgment of the Civil Cassation, Sec. labor, 6 March 2006, no. 4774, in particular, played an important role in the definition of the criminal case in Italy and linked it to Article 2087 of the Civil Code, stating that: "It can be carried out by material conduct or measures of the employer independently of the breach of specific contractual obligations provided for by the regulations of the employment relationship." This also implies the point of view of the Criminal Code about causing, in the employee victim of mobbing, personal injury (of the body or mind), or death events that may occur in the case of serious harassment perpetrated over time. Moreover, mobbing contradicts Legislative Decree 81/08 as amended, which establishes the employer's obligations to protect workers [11].

Workplace bullying is critical for its negative consequences on victims' health and well-being, which is why secondary and tertiary prevention interventions are the most widespread. Nevertheless, the aim is to prevent the phenomenon when it has not yet developed [12].

Primary preventive interventions should target organizational culture and climate, work organization and job design, workgroup functioning, and leadership effectiveness, reward systems, and competition, among the main ones [13].

For example, eliminating or reducing recognized hazards in the workplace is the foundation of the Total Worker Health® approach that promotes a hazard-free work environment, including bullying, for all workers. In particular, the "Hierarchy of Controls Applied to NIOSH Total Worker Health®" provides a conceptual model for prioritizing efforts to advance all workers' safety, health, and well-being [14].

However, in the literature, there is still very low-quality evidence that organizational and individual interventions may prevent bullying behavior in the workplace. We need large, well-designed, controlled trials of bullying prevention interventions operating on the levels of society/policy, organization/employer, job/task, and individual/job interface [15].

This systematic review assesses the prevalence of bullied workers in Italian workplaces. The target population will be the adult working population. We will assess the causes of the phenomenon, the correlation between exposure to bullying and physical and psychological consequences on workers, and the correlation between exposure to bullying and consequences at the organizational level.

2. Methods

A systematic review was conducted on adult workers to investigate the prevalence of bullying in Italian workplaces and verify causes and co-related effects. The review was recorded in PROSPERO, the international prospective register of systematic reviews, and the registration number is CRD 42023394635. The study was conducted per the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [16].

2.1. Search Strategy

Identification of studies relevant to this review was achieved by searching electronic databases of published literature, including PubMed, Scopus, and Web of Science. The keywords used on PubMed were: "workplace (bullying OR mobbing)" AND (Italian OR Italy). Scopus and Web of Sciences used the combination of two keywords: "workplace bullying" AND (Italian OR Italy) and "workplace mobbing" AND (Italian OR Italy). The search was undertaken with no language of publication restrictions. Articles search and data extraction was done between January 31, 2023, and March 1, 2023.

2.2. Study Selection

The review process was carried out using a multi-stage approach. Four authors conducted the selection and removal of duplicates independently [CC, DS, DG, II] and handled using ZOTERO. Then, after title and abstract screening, full-text articles were assessed to determine whether they met the inclusion criteria. If an included publication was unavailable as full text in English, the Corresponding Author was contacted to verify whether the eligibility criteria were met. Discrepancies and disagreements were discussed and resolved through a consensus session with a third-party researcher [GLT].

2.3. Inclusion and Exclusion Criteria

Inclusion criteria were as follows: i) studies involving workers in Italy; ii) the focus of the research is bullying; iii) the presence of information regarding the causes and consequences of the phenomenon. Exclusion criteria were: i) irrelevance to the research topic; ii) articles studying the phenomenon in other nations. There were no limits related to the publication date of the papers.

2.4. Data Extraction

Data extraction was conducted by four independent reviewers [CC, DS, DG, II], extracting data from all included studies. A data collection sheet was developed to confirm study relevance and to extract study characteristics. The following information was extracted from the studies: name of the first author, title, country, year of publication, study design, type of workplace, sample size, aim of the study, causes of the phenomenon, physical and psychological consequences, organizational consequences, assessment of the quality of the study. To ensure accurate data collection, each reviewer compared extracted data independently. Discrepancies and disagreements were discussed and resolved through a consensus session with a third-party researcher [GLT].

2.5. Quality Assessment

A quality assessment of the observational studies was carried out using the Newcastle-Ottawa Scale (NOS). This is a validated, easy-to-use scale of 8 items in three domains: selection, comparability, and exposure/outcome for case-control or cohort studies, respectively. Each item can be given one point, except comparability, which has the potential to score up to two points. Studies are rated from 0-9, with those studies rating 0-3 (poor quality), 4-6 (fair quality), and 7-9 (good/high quality). The NOS scale adapted for cross-sectional studies was used to assess the quality of cross-sectional studies [17]. This scale was a modified version of the NOS scale, as also used by several other studies that have felt the need to adapt the NOS scale so as to appropriately assess the quality of cross-sectional studies. Through a search of the literature, we found that a NOS score of 7 or more can be considered a "good" study [18, 19]. So, we used this criterion as a cut off for good quality study.

2.6. Statistical Analysis

A meta-analysis was conducted to assess the prevalence of bullied workers in Italy using the SPSS package version 27.0 (IBM Analytics, IBM Corporation, Armonk, NY, USA). Pooled prevalence of bullying was calculated only for studies in which the prevalence of bullying was reported or could be calculated. Studies were weighted by the number of participants. The prevalence of bullying was also calculated by considering only good-quality studies (NOS ≥ 7). In addition, a scatter plot was created to relate the prevalence of bullying and the degree of quality. Finally, the prevalence of bullying was also calculated by considering only studies related exclusively to the health sector.

3. Results

3.1. Search Results Summary

Research began in January 2023. The initial search across different electronic databases yielded 184 citations. First, a total of 68 duplicate papers were excluded, accompanied by the removal of 59 publications from the title/abstracts screening. Among the 57 full-text articles screened, 9 were not included. Finally, among the 48 articles selected and evaluated for eligibility, 6 reports were excluded because, upon further reading of the text, no useful correlations were found for our study. At the end of the process, 42 studies remained for qualitative analysis and 15 for quantitative analysis (Figure 1).

3.2. Characteristics of Included Studies

Forty-two studies were selected for our systematic review (Table 1). Publication dates ranged from 2006 to 2022. Regarding study design, 41 were cross-sectional and one was a cohort study with 92,036 workers.

The studies consider various workplaces, particularly public services (that included drivers, workers in airports, stations, etc.) with 19 studies, hospital and healthcare with 17 studies, private services with ten studies, public administration (that include municipality, local government, unions, etc.) with nine studies, university, and academia with four studies, industrial services with four studies; type of workplace was not specified in 8 studies. In assessing bullying risk, studies used different scales: the most widely used, in 22 studies, was the Negative Acts Questionnaire (NAQ), also in Short (S-NAQ) and Revised (NAQ-R) forms. The quality of each study was evaluated independently by four reviewers [CC, DS, DG, II] using the NOS scale: the lowest rating given was 4, the highest 8, with an average rating of 6.42.

3.3. Prevalence of Bullied Workers

Fifteen studies (Table 2) reported the aggregate prevalence of bullied workers. The median prevalence was 16.4% in studies scoring 8, 14.3% in those scoring 7, and 15.2% in those scoring 6. The prevalence in the study scoring 5 was lower (10.1%).

3.4. Causes of Workplace Bullying

There is not enough research to establish the causes of mobbing but that, if anything, the phenomenon is linked to a combination of factors, and it is unclear which is the cause and which is the effect. Assuming that bullying is independent of people's character and no credence can be given to theories that want to identify groups most at risk, in our work, we have categorized causes according to Zapf's subdivision [60], which investigated the

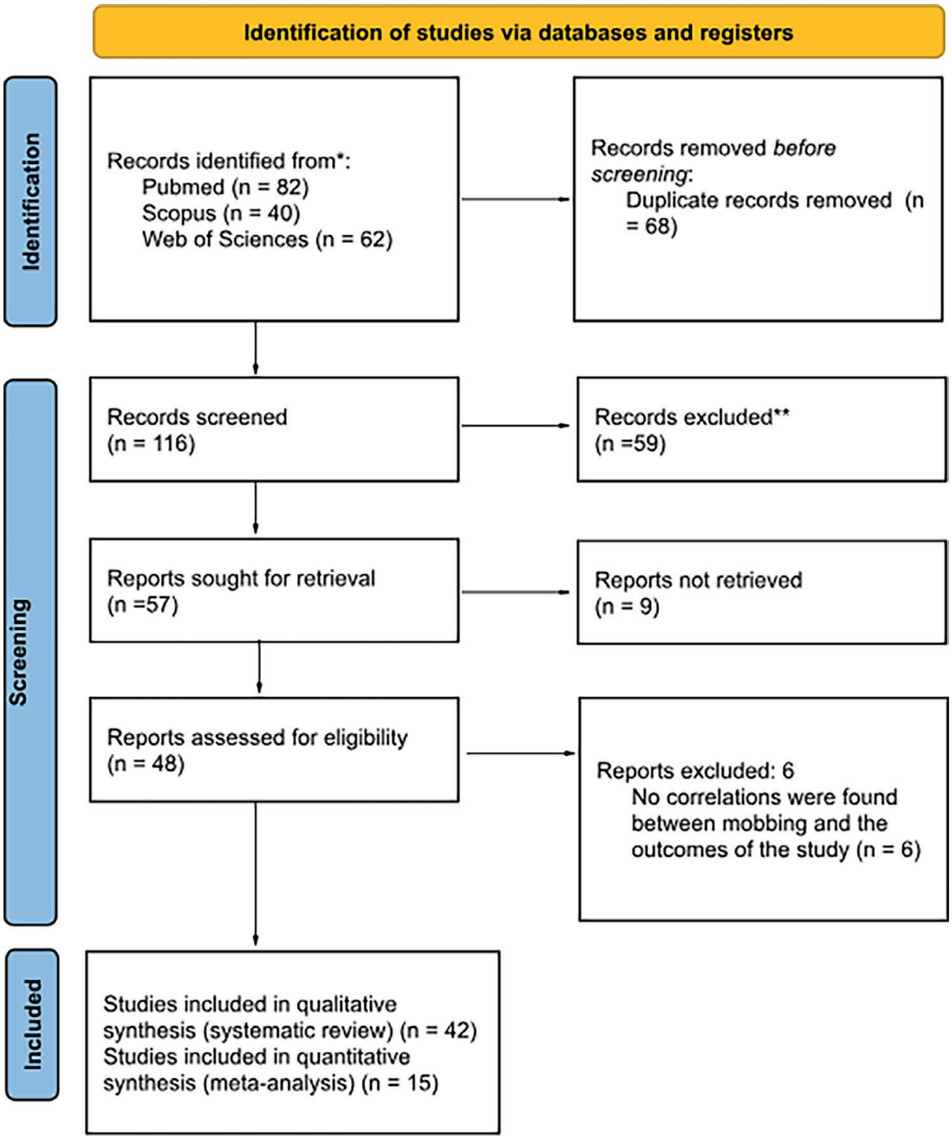

Figure 1. PRISMA 2020 Flow Diagram.

factors influential in the experience of mobbing behavior in Germany and found them to be factors concerning the social system of the working group and organizational factors.

Considering the forty-two articles selected (Table 3), only eight investigate the causes of workplace bullying. Of these eight articles, three identify social system and organizational causes [28, 30, 39], and five are only organizational causes [21, 24, 38, 57, 58]. From the perspective of social causes, victims of bullying suffer from gossip and rumors, being ignored/excluded, suggestions of dismissal, repeated reminders of mistakes or errors [39], unfair accusations, and emotional abuse [30].

Buselli et al. [28] reports the opportunist, authoritarian, and perverse personality of the bully, the unsuitable role of the manager, incompatible interpersonal relationships, and misunderstandings with the union as causes. Work organization also plays a key role in the causes of bullying. The high workload

Table 1. Characteristics of included studies and Quality Assessment.

1st Author[ref]	Year	Type of Workplace	No.	Bullying Scales	Quality (NOS)
Arcangeli et al. [20]	2014	Hospital and Healthcare	206	NAQ-R	8
Balducci et al. [21]	2020	Hospital and Healthcare	235	NAQ-R	6
Balducci et al. [22]	2009	Hospital and Healthcare, Public and Private Services	107	NAQ	7
Balducci et al. [23]	2012	Hospital and Healthcare, Public Administration	574	NAQ	6
Balducci et al. [24]	2015	Public Administration	609	NAQ-R	6
Balducci et al. [25]	2012	Public Administration	538	NAQ	7
Bambi et al. [26]	2018	Hospital and Healthcare	904	QuINI	7
Bambi et al. [27]	2014	Hospital and Healthcare	1202	LHQ	7
Buselli et al. [28]	2006	Public Services, Hospital and Healthcare	50	CDL	6
Campanini et al. [29]	2013	Public Services, Public Administration, Industrial Services, Private Services	8992	CDL	7
Caputo et al. [30]	2018	Public and Private Services	28	..	5
Chenevert et al. [31]	2022	Public Services	159	NAQ-R, S-NAQ	6
De Sio et al. [32]	2020	Hospital and Healthcare	191	HSE-IT	7
D'Errico et al. [7]	2011	Hospital and Healthcare, Public Administration, public Services	60763	..	6
Fadda et al. [33]	2015	University and Academic	221	NAQ-R	5
Fattori et al. [34]	2015	Hospital and Healthcare	755	..	6
Fenga et al. [35]	2012	Not Specified	63	LIPT Ege	5
Fiabane et al. [6]	2015	Not Specified	113	..	4
Fida et al. [36]	2018	Hospital and Healthcare	439	NAQ	6
Fida et al. [37]	2011	Hospital and Healthcare, Public Services	467	MOHQ	8
Finstad et al. [38]	2019	Industrial Services	512	NAQ-R	7
Giorgi et al. [39]	2011	University Services	3112	NAQ-R	6
Giorgi et al. [40]	2015	Industrial Services, Public Services	1393	NAQ-R	7
Giorgi et al. [41]	2015	Hospital and Healthcare	658	NAQ-R	8
Giorgi et al. [42]	2016	Industrial Services, Public Services	326	NAQ-R	6
Giorgi et al. [43]	2012	Public Services	371	UNICLIMA, NAQ-R	8
Giorgi et al. [44]	2009	University and Academic, Hospital and Health Care, Public and private services	926	NAQ-R, MDOQ10	8
Girardi et al. [45]	2007	Not Specified	160	..	5
La Torre et al. [46]	2022	Hospital and Healthcare	3129	WVHS	7
Lo Presti et al. [47]	2019	Not Specified	151	..	4
Nolfe et al. [48]	2010	Not Specified	707	..	6
Nolfe et al. [49]	2007	Hospital and Healthcare, Public Administration, Public and Private Services	533	..	5

1st Author[ref]	Year	Type of Workplace	No.	Bullying Scales	Quality (NOS)
Nolfe et al. [50]	2012	Not Specified	234	nQ-WD	8
Paciello et al. [51]	2019	Public and Private Services	1019	NAQ	8
Perbellini et al. [52]	2012	Not Specified	449	..	8
Punzi et al. [53]	2012	Public Services, Public Administration	100	CDL	8
Raho et al. [54]	2008	Not Specified	276	QAM	8
Romano et al. [55]	2007	Public Administration, Public and Private Services	500	LIPT Ege	4
Romeo et al. [56]	2013	Public and Private Services	48	..	5
Spagnoli et al. [57]*	2017	University and Academic	141	HSE-IT	6
Spagnoli et al. [58]	2017	Public and Private Services	134	S-NAQ	6
Vignoli et al. [59]	2015	Public Services	541	S-NAQ	7

**Cohort study.*
NAQ – Negative Acts Questionnaire; NAQ-R – Negative Acts Questionnaire-Revised; S-NAQ – Short Negative Acts Questionnaire; QuINI – Questionnaire on Negative interactions between nurses; LHQ – Lateral Hostility Questionnaire; CDL – Questionnaire on bullying action; HSE-IT – Health Safety Executive Indicator Tool; LIPT Ege – Leymann Inventory of Psychological Terror Ege Professional; MOHQ – Multidimensional Organizational Health Questionnaire; UNICLIMA - Organizational Climate Questionnaire; MDOQ10 – Majer D'Amato Organizational Questionnaire 10; WVHS – Workplace Violence in the Health Sector Country Case Studies Research Instruments Survey;nQ-WD – Naples Questionnaire Work Distress; QAM – Self-perceived bullying Questionnaire.

Table 2. Prevalence of bullied workers.

1st Author[ref]	Year	Sample Size	Prevalence of the Phenomenon	Absolute Number	Quality Assessment (NOS)
Arcangeli et al. [20]	2014	206	21.4 %	44	8
Balducci et al. [25]	2012	538	13.4%	72	7
Bambi et al. [26]	2018	904	15.2%	137	7
Bambi et al. [27]	2014	1202	22.4%	269	7
Campanini et al. [29]	2013	8992	7.2%	645	7
D'Errico et al. [7]	2011	60763	4.8%	2897	6
Fadda et al. [33]	2015	221	10.1%	22	5
Fattori et al. [34]	2015	755	16.3%	123	6
Fida et al. [37]	2011	467	5.0%	23	8
Giorgi et al. [39]	2011	3112	15.2%	473	6
Giorgi et al. [43]	2012	371	19.0%	70	8
Giorgi et al. [44]	2009	926	16.4%	152	8
La Torre et al. [46]	2022	3129	15.3%	478	7
Paciello et al. [51]	2019	1019	14.0%	143	8
Vignoli et al. [59]	2015	541	3.51%	19	7

Table 3. Causes of workplace bullying.

1st Author[ref]	Year	Causes of Workplace Bullying Social system	Organizational
Balducci et al. [21]	2020	..	Poor Working Conditions
Balducci et al. [24]	2015	..	Job Demands (Workload and Role Conflict) and Job Resources (Decision Authority, Co-Worker Support and Salary/Promotion Prospects)
Buselli et al. [28]	2006	Personality of the Bullying (Opportunistic, Authoritarian, Perverse), Manager Unfit; Incompatibility of Interpersonal Relations; Precarious Worker's Health Conditions; Misunderstandings with the Union	Company Restructuring/Changes at the Top; Non-Agreement on Company Procedures or Strategies;
Caputo et al. [30]	2018	Unjust Accusations, Emotional Abuse	Organizational Constraints, Treatment Discrimination, Job Duty Changes, Precariousness, Lack of Recognition, Feeling of Exclusion and Job Disengagement
Finstad et al. [38]	2019	..	Workload, Lack of Control, Lack of Support
Giorgi et al. [39]	2011	Gossip And Rumors, Being Ignored/ Excluded, Hints to Quit, Repeated Reminders of Errors or Mistakes (Private > Public)	Unmanageable Workload (Public > Private)
Spagnoli et al. [57]	2017	..	Workload, Psychological Strain, Organizational Change
Spagnoli et al. [58]	2017	..	High Workload

[38, 57, 58], psychological tension, organizational change [57], organizational constraints, discriminatory treatment, job changes, precariousness, lack of recognition, sense of exclusion, job disengagement [30], poor working conditions [21], lack of control and support [38], corporate restructuring, changes at the top and failure to agree on procedures or business strategies [28] can be classified as organizational causes.

3.5. Physical and Psychological Consequences

Of the forty-five articles reviewed, thirty-two highlight the physical and psychological consequences of workplace bullying (Table 4). Of these, two highlight only physical consequences [43, 59], and eighteen highlight only psychological consequences [20, 22, 23, 30-33, 35, 38, 41, 42, 48-51, 55, 56]. Twelve identify both types [6, 45, 53, 23, 26-28, 34, 37, 47, 52, 54]. Prolonged bullying has been associated with worsening the victim's quality of life, leading to physical and psychological consequences causing permanent problems [34, 37, 43]. Among the physical consequences, pathologies affecting the gastrointestinal system, such as colitis, irritable colon, and diarrhea, have been found [6, 23, 26, 28, 52]; affecting the nervous system, such as headaches, the feeling of diffuse muscle tension [26, 28, 52], choking sensation [26, 28], panic attacks [28]; dizziness and paresthesia [28]; excessive food consumption or loss of appetite [26, 28, 52]; affecting the muscular system with disorders of the lower back, upper back and neck [59]; affecting the cardiovascular system with tachycardia, chest oppression and chest pain [26, 27, 52]; sleep disorders such as insomnia, sleepiness and tiredness upon waking [53, 26]. Bambi et al. [26] also finds apathy and depression resulting in reduced concentration at work [26, 54]. Decreased libido can also be classified as a physical but also psychological consequence [28]. Regarding

Table 4. Physical and psychological consequences.

1st Author[ref]	Year	Individual consequences: Physical	Individual consequences: Psychological
Arcangeli et al. [20]	2014	..	Loss of Self-Confidence, Social Consequences, Depression, Anxiety
Balducci et al. [22]	2009	..	Neurotic Component (Hypochondriasis, Depression, Hysteria) and Paranoid Component, Posttraumatic Stress Disorder, Suicidal Ideation and Behavior
Balducci et al. [23]	2012	..	Depressive Disorder
Balducci et al. [25]	2012	Irritable Bowel Syndrome	Psychological Distress, Depression
Bambi et al. [26]	2018	Chronic Fatigue, Gastrointestinal Disorders, Apathy, Reduced Concentration During Worktime, Headaches, Depression, Diffuse Muscular Tension, Excessive Food Consumption, Reduced Appetite, Sensation of Difficult Breathing, Chest Pain, Palpitations	Anxiety, Sleep Disorders, Irritability and Anger, Susceptibility, Sensation That the Working Life Exerts Negative Influences on the Private Life, Reduced Self-Esteem, Fear of Going to the Workplace, Lack of Desire to Go to the Workplace, Frequent Flashbacks About the Episodes of Abuse, Sensation of Remoteness/Alienation, Frequent Feeling of Guilty, Increased Consumption of Tobacco, Alcohol and Drugs
Bambi et al. [27]	2014	Chronic and Cardiovascular Illnesses, Psychosomatic Symptoms	Generally High Stress Levels, Reduced Self-confidence, Psychological Symptoms, Reduced Work Satisfaction
Buselli et al. [28]	2006	Decreased Libido, Tachycardia, Chest Oppression, Panic Attacks, Poor Sleep Quality (Insomnia, Sleepiness), Headache, Feelings of Suffocation, Gastralgias, Paresthesias, Dizziness, Diarrhea, Loss Of Appetite, Drug Addiction	Decreased Libido, Concentration Deficit, Irritability, Asthenia, Anxiety, Mood Disorders, Social Withdrawal
Caputo et al. [30]	2018	..	Job Disengagement (Affective Detachment and Powerlessness in Accomplishing Duties)
Chenevert et al. [31]	2022	..	Neuroticism
De Sio et al. [32]	2020	..	Worse Perception of Psychosocial Risks
Fadda et al. [33]	2015	..	Mental Health Problems
Fattori et al. [34]	2015	Worse Health-Related Quality-of-Life Scores (Above and Beyond the Effect of Concurrent Medical Conditions)	Worse Health-Related Quality-of-Life (Above and Beyond the Detrimental Effect of Other Concurrent Medical Conditions)
Fenga et al. [35]	2012		Depression, Hysteria, Paranoia
Fiabane et al. [6]	2015	Dyspnea, Palpitations, Gastrointestinal Diseases	Mood Disorders; Insomnia; Panic Attacks, Sleep Disturbances, Social Dysfunction, Post-Traumatic Stress Disorder
Fida et al. [37]	2011	Health Symptoms	Negative Emotions, the Three Discrete Emotions (Anger, Fear, And Sadness), Moral Disengagement

Table 4 *(continues)*

Table 4. Physical and psychological consequences.*(continued)*

		Individual consequences	
1st Author[ref]	**Year**	**Physical**	**Psychological**
Finstad et al. [38]	2019	..	General Health (Anxiety, Loss of Security, Social Dysfunction)
Giorgi et al. [40]	2015	..	Job Dissatisfaction, Particularly Among Blue Collars; Women Reported Less Psychological Well-Being Than Men; Blue-Collar and White-Collar Employees Reported Less Mental Health Than Managers
Giorgi et al. [42]	2016	..	Psychological Distress (Workplace Bullying Was Indirectly Negatively Associated with Self-Management Ability Via Increased Psychological Distress)
Giorgi et al. [43]	2012	Health Problems	..
Girardi et al. [45]	2007	Somatic Symptoms	Depressed Mood, Difficulty in Making Decisions, Change-Related Anguish, and Passive-Aggressive Traits, Need for Attention and Affection.
Lo Presti et al. [47]	2019	Physical Negative Symptoms	Psychological Negative Symptoms (Anxiety and Depression)
Nolfe et al. [48]	2010	..	Anxiety Disorders, Mood Disorders and Adjustment Disorders
Nolfe et al. [49]	2007	..	Adjustment Disorders, Anxiety Disorders (Post-traumatic Stress Disorder) and Mood Disorders (Depression)
Nolfe et al. [50]	2012	..	Mood Disorders, Anxiety Disorders, Mainly Somatoform
Paciello et al. [51]	2019	..	Negative Emotions (Fear, Anger, Sadness), Disengagement and Compensatory Behavior
Perbellini et al. [52]	2012	Sleep Disorders, Gastrointestinal Problems, Eating Disorders, Cardiovascular Disorders	Post-Traumatic Disorder, Chronic Adjustment Disorder
Punzi et al. [53]	2012	Fatigue Upon Waking, Frequent Awakenings, Muscle Tension, Antidepressant Use	Depression, Anhedonia
Raho et al. [54]	2008	Difficulty at Work	Anxiety, Obsession, Depression, Anger, Antisocial Behavior, Family Problems
Romano et al. [55]	2007	..	Depressive State
Romeo et al. [56]	2013	..	Hypochondria, Depression, Hysteria, Paranoia, Suicidal Ideation (Common Among Victims)
Vignoli et al. [59]	2015	Musculoskeletal Disorders of The Low Back, Upper Back and Neck	..

the consequences on a psychological level, Fattori A [34], highlights an important deterioration in the quality of life linked to bullying in the workplace.

Health issues include negative emotions such as anger, fear and sadness, moral [26, 37] and occupational [30] disengagement, fear of going to work, lack of desire to go to work, frequent flashbacks on the episodes of abuse [26], psychological and social distress [20, 26, 28, 32, 38]; lower self-management skills, reduced self-esteem, difficulty in making decisions, anxiety related to change and passive-aggressive traits resulting in a need for attention and affection [4, 20, 27, 40, 42]. Bullying also causes mental health problems such as anxiety disorders, mood and adjustment disorders, attention difficulties, hypochondria, depression, hysteria and paranoia, suicidal ideation and behavior, neuroticism, post-traumatic stress disorder, chronic adjustment disorder, anhedonia, psychosomatic and stress disorders [6, 53, 20, 22, 23, 25, 27, 28, 31, 33, 35, 38, 47-56]. Drug addiction, antidepressant use, and increased tobacco use can be identified in both groups of consequences [53, 26, 28].

3.6. Organizational Consequences

Analyzing the forty-five selected articles, ten report organizational consequences of workplace bullying. Three studies [7, 29, 34] highlight how absenteeism in the workplace is a frequent consequence of bullying, while two of them [6, 27] describe it as a consequence of the victim's desire to change departments or jobs (Table 5). This leads to a loss of productivity through absenteeism [34] and a distorted perception of workers as invisible, interchangeable, and unnecessary, thus contributing to their affective detachment from work contexts [30]. The worker then reports making mistakes while at work [26]. Giorgi [43] investigates how bullying affects the organizational climate by interfering with work, autonomy, communication, and development. Finally, Giorgi [41] showed an indirect relationship with burnout.

4. Discussion

This systematic review aimed to assess the prevalence of the phenomenon in the Italian workplace and to investigate the causes and consequences it has on the physical and psychological health of the worker as well as on the organization. The average prevalence of bullied workers in Italian workplaces was 11.9%, excluding D'Errico's [7] study, and 6.7%, including this large study. Considering only good-quality studies, the prevalence was 11.2%, rising to 17.0% if only studies conducted in the health sector

Table 5. Organizational consequences.

1st Author	Year	Organizational Consequences
Bambi et al. [26]	2018	Reported Making Errors During Work
Bambi et al. [27]	2014	Change Departments/Services of Assignation
Campanini et al. [29]	2013	Sickness Absence
Caputo et al. [30]	2018	Workers Perception of Being Progressively Invisible, Interchangeable, Unnecessary, Thus Contributing to Their Affective Detachment from Work Contexts
Chenevert et al. [31]	2022	Role Conflict Influences Posttraumatic Stress Disorder Symptomology Through Exposure to Bullying, Which Differs Based on the Level of Managerial Competencies
D'Errico et al. [7]	2011	Sickness Absence
Fattori et al. [34]	2015	Productivity Losses (Absenteeism and Presenteeism)
Fiabane et al. [6]	2015	Change Of Job or Department
Giorgi et al. [43]	2012	Workplace Bullying Influenced Organizational Climate (Job Description, Autonomy, Development, Communication, Job Involvement)
Giorgi et al. [40]	2015	Workplace Bullying Partially Mediated the Climate-Burnout Relationship and Influenced Health Only Indirectly

were considered. Regarding the prevalence of the phenomenon worldwide, a meta-analysis, in which samples from twenty-four different countries and a multinational sample were represented, reports an overall prevalence of 14.6% [61]. Among European countries, from a survey conducted in 2000, Finland shows the highest rate (15%), followed by the Netherlands and the United Kingdom with a rate of 14%, Sweden 12%, Belgium 11%, France and Ireland 10%, Denmark 8%, Germany and Luxembourg 7%, Austria 6%, Spain and Greece 5%, Italy and Portugal 4% [62]. Workplace bullying has also been prevalent in non-European countries, e.g., in Japan, the reported rate is 15% [43].

The prevalence rates of workplace bullying vary considerably depending on cultural and geographical characteristics, the method used to detect it, and the work environment investigated. Considering only the studies conducted in the healthcare sector, this systematic review revealed a much higher prevalence (17%). This result is very important and in line with other studies in the literature according to which employees in the healthcare sector have a high risk of exposure to workplace bullying [63-66]. According to Kingma [67], people working in the health sector, in particular, doctors and nurses, have a sixteen times higher risk of being exposed to negative behavior than in other work sectors; the risk for nurses is also three times higher than for other employees in the health service.

A recent cross-sectional study conducted in Italy reported a prevalence of 15.3% among health workers, with nurses being the most affected category. According to this study, no significant differences exist in the phenomenon's prevalence among the department healthcare workers belong to [46]. Another study also points out that the professional category of nurses is particularly at risk of bullying, without any demographic or gender differences [20]. Although no type of healthcare worker can be considered free from this risk, as shown by most studies investigating this phenomenon, the most at-risk departments are emergency and psychiatry [68-71] and radiology and infectious diseases [68, 72-74].

The scientific literature often focuses on detecting the phenomenon and the consequences in terms of the victim's quality of life. Still, it is equally important to identify the causes to be able to intervene preventively.

Regarding the causes of workplace bullying, it was found that only a low number of them investigate this aspect. In discussing these issues, it is important to premise that there is a difference between finding a cause, what our work is intended to achieve, and attributing blame or responsibility. Leymann and other authors make a critique against all those who identify victims as having "problems" or inherent character frailties. Rather, bullying directly expresses a pathology of production and decision-making processes within companies and workplaces [75].

Considering this, in analyzing the causes of the phenomenon, we have considered social and organizational factors. The work environment and the social context can be factors that favor the presence of the phenomenon. A worker subjected to unfair accusations, emotional abuse, gossip, repeated reprimands, and suggestions of dismissal, who is excluded from his or her work environment, or who has misunderstandings with his or her union affiliation is at high risk of frustration resulting in bullying attacks. A study conducted in Germany confirms how exposure to the demands and pace of work is correlated with an increased risk of being exposed to bullying. In contrast, job resources, including leadership quality and job influence, acted as protective factors [76].

Among organizational causes, particular importance is given to the high workload of employees, which can generate role conflict and psychological tension among colleagues. Organizational change, corporate restructuring, and failure to agree on strategies and procedures are all triggers. Workers who have high prospects for pay or promotion or who, on the contrary, do not get the recognition they deserve or who suffer discrimination may face harassment. Numerous studies have considered psychosocial risks related to work organization as the main cause of bullying, highlighting how certain elements of organizational design could act as barriers and drivers [77, 78].

The victim of bullying then has a worsening quality of life with both physical and psychological consequences. The physical consequences that are most commonly described are gastrointestinal system disorders such as irritable bowel syndrome, diarrhea, and loss of appetite, cardiovascular system disorders that may result in disease and/or chronic. Apathy, continuous headaches, dizziness, impaired sleep quality, chronic fatigue, reduced concentration, and libido seem to be other common consequences. Work-related stressors could activate the brain aging process, leading to cognitive impairment with a risk of dementia and Alzheimer's disease. One study reviewed looks at brain changes demonstrating decreased hippocampal volume in major depressive disorder [79].

Regarding the psychological aspect, we found several consequences related to mental health problems such as depression, anxiety, hysteria, post-traumatic stress disorder and mood disorders, suicidal behavior, paranoia, and repeated irritability and anger. The individual may face social consequences and lower job satisfaction. Studies reviewed also report increased alcohol and psychotropic drug use as both physical and psychological consequences.

Finally, the organizational consequences of workplace bullying were assessed in our work. A strong presence of absenteeism was highlighted, which can sometimes take the form of departmental change to the point of job change, particularly in the healthcare sector. This mode of action was found to be similar in an Australian study in which bullied healthcare workers initially absented themselves from duty in an attempt to recover; the next coping strategy was calling in sick or not showing up for work at all, and finally if the bullying persisted, resignation [80]. Our study also found that such absenteeism results in a loss of productivity and quality of work. Concerning healthcare workers, this aspect was also highlighted in a Swedish study in which it was shown how not only being bullied but also being a bystander can have consequences on the job and the organization, affecting the perceived quality of care, employees' work commitment and their intention to leave the organization [81]. Bullied workers also report feeling unnecessary or even invisible in the workplace. Indeed, in the literature, although the most important effects of bullying and harassment are arguably found at the individual level (ranging from increased anxiety and reduced job satisfaction to symptoms of depression and burnout) [82], it has also been noted that bullying and harassment may be expected to hamper various variables at the work unit and organizational levels. Where bullying and harassment impede job satisfaction or internal cooperation, it is likely that factors such as turnover and absenteeism will be heightened, impeding the organization's functioning [83].

4.1. Strengths and Limitations of the Study

This review aims to provide an overview of the bullying situation in Italy, trying to assess what could be the causes of this phenomenon and its consequences. Since the study was based on cross-sectional studies, it does not claim to identify any causal inference but to report the consequences and causes most frequently reported in the literature. Another review by D'Assisti et al. [7] examines the phenomenon of bullying in the Italian workplace and focuses on gender differences and the characterizations and ways in which they are committed. Our article aims to have a broader scope in describing the bullying phenomenon: in fact, in our review, several aspects were considered, not only the prevalence but also the causes, the consequences on workers and the organizational ones. Another strength of our study is the quality of the studies considered, which is moderate. The review, however, is subject to limitations. The first limitation is related to the fact that the causes and consequences extrapolated from the articles were formulated based on questionnaires filled out by employees of the various companies. The causes are those indicated or hypothesized by workers but not proven. Similarly, the consequences are those that might occur or that, in some studies, are associated with the experience of violence. In addition, the prevalence we found is not that of cases of bullying but that of workers complaining of being mistreated, as the authors of the articles do not point out to us that these situations have occurred. Secondly, the general prevalence refers to different survey and selection methods and different working environments: it must be considered that employees in the workplace can more or less perceive the condition of bullying based on their sensitivity and culture. for example, the prevalence is higher in European countries where civil rights are more guaranteed [84]. Thirdly, it should be noted that, as reported by numerous studies and reviews, professionals are not interested in reporting violence for a variety of reasons but mainly due to previous experiences of no subsequent/successful action or fear of the consequences and lack of management support [85, 86, 87, 88] so the calculated prevalence may be underestimated. Finally, we need to recognize that some evidence was retrieved from papers that were published as abstracts of Occupational medicine Congresses, that usually do not follow a rigorous peer review process.

5. Conclusions

Bullying in Italian workplaces is far from negligible, particularly in hospitals. Companies should develop strategies to prevent it, reducing or eliminating the risk and enabling the acquisition of skills by workers to manage and evaluate these events when they occur.

Declaration of Interest: The Authors declare no conflict of interest.

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