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Artificial Intelligence and Occupational Health and Safety, Benefits and Drawbacks

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Summary

This paper discusses the impact of artificial intelligence (AI) on occupational health and safety. Although the integration of AI into the field of occupational health and safety is still in its early stages, it has numerous applications in the workplace. Some of these applications offer numerous benefits for the health and safety of workers, such as continuous monitoring of workers' health and safety and the workplace environment through wearable devices and sensors. However, AI might have negative impacts in the workplace, such as ethical worries and data privacy concerns. To maximize the benefits and minimize the drawbacks of AI in the workplace, certain measures should be applied, such as training for both employers and employees and setting policies and guidelines regulating the integration of AI in the workplace.

1. Introduction

In 1955, John McCarthy was the first to create the term 'Artificial Intelligence' (AI) [1]. AI refers to the simulation of human intelligence in machines that are programmed to think and learn like humans. It involves the development of algorithms and computational models that enable machines to perform tasks traditionally requiring human intelligence. These tasks include problem-solving, speech recognition, decision-making, visual perception, language translation, and more [2].

AI can be divided into two primary categories: Internet of Things (IoT) optimized for specific tasks and performs well in voice assistants, recommendation algorithms, and image recognition systems [1, 2] and generative AI, i.e., systems that associate words, learn, and solve complicated issues but, despite their name, are not as intelligent as human beings [2, 3]. AI comprises several subfields, such as robotics, computer vision, natural language processing, machine learning, and expert systems. AI mostly relies on machine learning, which uses algorithms to allow computers to learn from experience, providing "intelligent" outcomes without explicit programming [4].

On the other hand, occupational health and safety (OHS) is defined as a multidisciplinary field concerned with safeguarding and promoting the well-being of individuals in the workplace. It encompasses a systematic approach to identifying, assessing, and mitigating risks and hazards that may arise from work-related activities [5]. The primary goals of OHS are to prevent injuries, illnesses, and fatalities among workers and to create and maintain a work environment fostering the workers' physical, mental, and social health [6].

Currently, AI enables real-time monitoring of workplace hazards, identifying and addressing risks

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proactively, and enhancing preventive measures through predictive analytics powered by AI forecasts health trends [4, 7, 8]. The incorporation of AI not only improves safety protocols but also advances a comprehensive approach to employee well-being, marking a paradigm shift in the field of OHS with increased efficiency and precision [9, 10]. On the other side, innovative uses of AI in the workplace provide significant challenges for OHS professionals who need to gain a deeper grasp of AI approaches and their possible consequences on work and workers when AI-enabled apps are implemented in the workplace [2, 3, 11, 12]. As AI technologies are used in the workplace, it is imperative to maximize their potential benefits for OHS while minimizing any potential drawbacks.

2. Benefits and applications of AI in Occupational Health and Safety

2.1. Worker's Health Monitoring Through Wearable Devices, Sensors and IoT Devices

Wearable devices and sensors in the workplace are pivotal in enhancing workers' well-being, safety, and overall productivity [13]. These devices are commonly used to monitor various health metrics, including vital signs, steps taken, and sleep patterns, identify fatigue or stress levels, and promptly notify workers and supervisors in case of emergencies or potential health risks [13-15]. IoT refers to the network of interconnected physical devices, objects, and systems that communicate and share data through the Internet [16]. In a workplace context, IoT involves embedding various sensors and other smart devices into the infrastructure to collect and exchange data [17]. Numerous studies have indicated that companies can utilize data from wearable devices, sensors, and IoT, enhanced by AI, to identify potential health risks such as elevated stress levels or irregular sleep patterns [14, 15, 18-20]. Moreover, the data collected by wearable devices and IoT can be manipulated by AI to inform the implementation of targeted wellness programs, including personalized fitness plans and stress management workshops, to support overall employee well-being [15, 21]. In hazardous work environments like construction, mining, and manufacturing, specialized wearable devices such as smart helmets equipped with sensors can detect harmful gases, monitor environmental conditions, and assess head injuries [22]. These wearables, integrated with AI, trigger automatic alerts or emergency responses in case of accidents, ensuring timely assistance and preventing severe consequences [23]. Hence, the integration of wearables, sensors, and artificial intelligence empowers both employers and employees to prioritize health and safety, resulting in increased productivity, reduced absenteeism, and enhanced job satisfaction [3, 7]. As these technologies advance, we can anticipate even more sophisticated applications that will reshape the landscape of workplace health monitoring in the future.

Sensor technology extends beyond wearables to workplace health monitoring, with environmental sensors throughout workspaces detecting factors like temperature, humidity, noise levels, and air quality [24, 25]. When coupled with AI-driven systems, these sensors evaluate overall workplace health and safety, identifying potential hazards and proactively improving conditions [22, 26].

2.2. Smart Building Systems for Energy Efficiency and Employee Comfort

AI can optimize smart building systems to enhance energy efficiency while maintaining optimal conditions for employee comfort [27]. This includes intelligent climate control, lighting, and resource management in the workplace [26, 28].

2.3. Hazard Identification and Risk Assessment

Hazard detection programs help protect against various risks, such as unsafe working conditions, workers without protective clothing, misuse of tools and equipment, trip and fall hazards, unattended vehicles, equipment out of place, and other compliance issues [29-31]. Industries can employ AI systems to examine images and videos from workplaces, uncovering potential hazards that may elude human observation [29, 32]. For example, the UK's Health and Safety Executive developed an artificial intelligence program called Estimation and

Assessment of Substance Exposure (EASE) to assess occupational exposure to certain substances in the workplace [32]. Additionally, AI can play a role in forecasting machinery breakdowns. Through the analysis of sensor data on machines, AI can identify abnormal patterns that signal a potential fault [1]. This proactive detection enables companies to perform maintenance before a machine malfunctions, averting potential accidents. Moreover, AI programs can identify, assess, and mitigate risks by analyzing data and identifying patterns and anomalies [16, 32]. However, few studies have been conducted to demonstrate the positive and negative aspects of integrating AI into the risk assessment process and health surveillance in workplaces. This might be because the integration of AI in the industry is still in its early stages, and the main current focus is on its impact on immediate concerns such as safety and regulatory compliance [4, 10, 29].

2.4. AI-Integrated Smart Personal Protective Equipment

Personal Protective Equipment (PPE), such as respirators, safety shoes, ear muffs, and safety goggles, has always played a crucial role in safeguarding workers from various hazards in the workplace [33]. When a task poses inherent risks that cannot be sufficiently controlled through collective technical or organizational measures, the use of PPE becomes essential to enable workers to perform their tasks with reduced injury risks [5]. The reliability and effectiveness of PPE are paramount, aligning with the established principle of the hierarchy of prevention.

Smart PPE refers to PPE that combines traditional PPE (such as firefighter protective suit) with electronics, such as sensors, detectors, data transfer modules, batteries, cables, and other elements [22, 34]. By combining AI technologies with smart PPE, it actively monitors and adapts to changing environmental conditions, detecting hazards, assessing air quality, and providing real-time alerts [22, 34, 35]. This innovation enhances communication and fosters a proactive approach to occupational safety, ensuring a safer work environment across diverse industries.

2.5. Workplace Violence Monitoring

Workplace violence is a pervasive issue globally that poses a risk to workers' mental health. More than one in five people (almost 23 %) in employment have experienced violence and harassment at work, whether physical, psychological or sexual [36]. AI can play an important role in preventing workplace violence. Natural language processing (NLP) is a technique from computer science that helps to analyze large bodies of text. Using NLP, AI can scan emails and files for inappropriate language, alerting managers when such phrases are detected [37, 38]. With voice recognition, AI can recognize spoken phrases in meetings, generating detailed reports to address instances of harassment [36, 39, 40].

2.6. AI in Drug and Alcohol Screening Programs

About 60% of people with substance use disorders (SUDs) are currently employed [41]. Hence, workers' alcohol and drug use can harmfully impact both the workers and the workplace, resulting in absenteeism, high turnover, decreased productivity, and other safety problems [42]. AI can contribute to more efficient and accurate drug and alcohol screening processes in the workplace [43]. Automated systems can analyze biological samples, ensuring compliance with safety regulations and promoting a substance-free work environment [43, 44].

2.7. Workforce Mental Health Monitoring

AI-driven tools are increasingly employed for monitoring and addressing mental health issues in the workplace, which can be done using remote health monitoring systems by tracking vital signs and health metrics and providing real-time information to healthcare professionals for early detection of health issues among workers [4, 45]. In addition, NLP can play a role in analyzing workers' communication for signs of stress, enabling timely interventions and support [38]. This enables organizations to implement preventive measures to support workers' mental health and well-being.

In their literature review, Moshawrab et al., 2022, discussed the importance of using AI-integrated

smart wearable devices to screen and identify occupational physical fatigue among workers [13]. They reported that AI-integrated smart wearables have established their usefulness in identifying and screening fatigue at work, which can limit the harmful effects of fatigue on workers [13].

2.8. Musculoskeletal System and Ergonomics

The work-related musculoskeletal disorders (WMSDs) are considered an important cause of occupational injury at the workplace, leading to increased absence rates from work [46, 47]. On the other hand, ergonomics can defined as adjusting work environments, tools, and worker postures to prevent WMSDs induced by ergonomic risk factors such as awkward posture, repetitive movements, and excessive force at work [48, 49]. Ergonomists usually assess each worker's ergonomic risk factors using techniques such as postural analysis, anthropometric measures, motion and time studies, biomechanical models, force evaluation, and energy expenditure assessments [48, 50]. Recently, several studies have shown the possibility of improving ergonomic analysis through the combined use of artificial intelligence and wearable sensors [26, 51-53]. AI-assisted health programs can analyze ergonomic factors and individual anthropometric data to predict and prevent musculoskeletal disorders in the workplace [51]. AI-driven wearable devices can continuously analyze workers' motions and body postures [52] to recognize movements that may pose a risk of injury. Alerts are then issued to workers to mitigate the potential for long-term health problems [53].

2.9. Automating Dangerous Tasks Using AI Automated Bots

Bots, short for robots, are automated software programs designed to perform specific tasks. The most important bots used in industry are collaborative robots (Cobots) and Chatbots. Collaborative robots, often referred to as cobots, are designed to work in close proximity to humans, fostering a collaborative and cooperative environment [54, 55]. Unlike traditional industrial robots that operate in isolation or behind safety barriers, cobots are engineered to share the workspace with human operators [3]. This collaboration aims to enhance productivity and safety in sectors such as manufacturing and logistics [3]. Chatbots are bots designed to engage in conversation with users, and they are commonly used in customer service, providing quick and automated responses to queries [55]. Automation through AI and Machine Learning (ML) enhances the efficiency of robots, particularly in handling hazardous tasks, including safety inspection of hazardous environments, maintenance, and handling of dangerous materials [55, 56].

2.10. AI-Enhanced Occupational Health Compliance Safety Audits

By using IoT sensors, AI can track and audit every individual worker on multiple levels, ensuring that workplaces adhere to safety standards, minimize legal risks, and promote a culture of compliance [16]. This includes monitoring worker locations, tracking vital signs, alerting workers to environmental hazards, providing accurate information to remote workers, reducing the risk of physical injuries, and enhancing staff training [7, 16, 24].

2.11. Decision Support Systems (DSS)

Decision support systems (DSS) are computer-based tools or systems that support decision-making activities within an organization [57]. They provide interactive access to databases and help users analyze complex data, generate reports, and make decisions based on the insights gained [58]. AI-powered DSS can assist managers and executives in making informed decisions by analyzing complex data sets, identifying patterns, and providing insights and recommendations [3, 7]. These systems leverage techniques like data mining, machine learning, and NLP to aid decision-making across various industries [57, 59].

3. Drawbacks and Ethical Issues of AI in Occupational Health and Safety

Despite AI's immense potential to enhance workplace safety, its implementation brings challenges

and ethical issues. Developing and implementing AI systems can be expensive and may require significant investment in hardware, software, and training [3, 7].

High-quality data is essential for AI to make accurate risk assessments and envisage effective recommendations. If the data used is incomplete, outdated, or inaccurate, it can significantly impact the performance of the AI system, which could result in erroneous predictions and potentially lead to safety hazards [12]. Similar to humans, AI is susceptible to amplify bias if it is trained on biased data. So, it is imperative to ensure that AI systems are trained on balanced and representative data to mitigate such biases [60].

3.1. AI-Related Ethical Issues at the Workplace

Artificial intelligence can potentially revolutionize health and safety practices, introducing ethical considerations that must be addressed. Critical ethical issues include ensuring privacy and data security, given that AI systems rely on extensive datasets containing personal information such as wearable devices and sensors [12, 60, 61]. So, it is essential to guarantee this data's ethical and secure collection, utilization, and storage. Additionally, concerns arise regarding biases and discrimination inherent in AI systems stemming from the data on which they are trained, leading to potential unfair or discriminatory decision-making [4, 12, 62]. Furthermore, the automation capabilities of AI raise apprehensions about job displacement, prompting considerations about the necessity for safety professionals to acquire new skills in response to evolving tasks [12, 63, 64].

3.2. AI-Impacts on Worker's Mental Health

Integrating AI in health and safety could negatively impact workers' mental health, including anxiety and stress related to job automation or the potential for AI errors to lead to accidents [4, 11, 65, 66]. Workers may feel a loss of control in an environment monitored by AI systems, experience isolation and disconnection from human colleagues when interacting more with AI, and perceive a diminishing sense of meaning and purpose when their tasks are automated by AI [4, 66, 67]. Recognizing and addressing these emotional impacts is essential to creating a positive and supportive work environment while implementing AI technologies. Considering the role of occupational physicians excluded from algorithm definitions and the potential organizational and evaluation implications arising from such exclusion is of utmost importance. This brings attention to the critical intersection between healthcare professionals, technology, and regulatory frameworks, emphasizing the significance of including occupational doctors in discussions around AI implementation and compliance with existing laws and regulations.

4. Conclusion

In conclusion, integrating AI in occupational health and safety offers benefits such as enhanced safety and productivity through predictive maintenance and real-time risk assessment. However, drawbacks include ethical concerns, data privacy considerations, and the need for regulatory compliance. Work organizations must balance innovation with respecting workers' rights, investing in workforce education, building AI expertise, and collaborating with solution providers to seamlessly ensure a safe workplace that integrates AI and human ingenuity.

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References

1. Howard J. Algorithms and the future of work. *Am J Ind Med*. 2022;65(12):943-952. Doi: 10.1002/ajim.23429
2. Georgieff A, Hyee R. Artificial Intelligence and Employment: New Cross-Country Evidence. *Front Artif Intell*. 2022;5:832736. Doi: 10.3389/frai.2022.832736
3. Howard J. Artificial intelligence: Implications for the future of work. *Am J Ind Med*. Nov 2019;62(11): 917-926. Doi: 10.1002/ajim.23037

4. Niehaus S, Hartwig M, Rosen PH, Wischniewski S. An Occupational Safety and Health Perspective on Human in Control and AI. *Front Artif Intell*. 2022;5:868382. Doi: 10.3389/frai.2022.868382
5. Rieth LK. The occupational health service. Staffing, facilities, and equipment. *AAOHN J*. Aug 2000;48(8): 395-403; quiz 404-5.
6. Castillo C, Shahriari M, Casarejos F, Arezes P. Prioritization of leading operational indicators in occupational safety and health. *Int J Occup Saf Ergon*. 2023;29(2): 806-814. Doi:10.1080/10803548.2022.2082693
7. Pishgar M, Issa SF, Sietsema M, Pratap P, Darabi H. REDECA: A Novel Framework to Review Artificial Intelligence and Its Applications in Occupational Safety and Health. *Int J Environ Res Public Health*. 2021;18(13). Doi: 10.3390/ijerph18136705
8. Carbonero F, Davies J, Ernst E, Fossen FM, Samaan D, Sorgner A. The impact of artificial intelligence on labor markets in developing countries: a new method with an illustration for Lao PDR and urban Viet Nam. *J Evol Econ*. 2023:1-30. Doi: 10.1007/s00191-023-00809-7
9. Djebrouni M, Wolbring G. Impact of robotics and human enhancement on occupation: what does it mean for rehabilitation? *Disabil Rehabil*. 2020;42(11):1518-1528. Doi: 10.1080/09638288.2018.1527401
10. Hazarika I. Artificial intelligence: opportunities and implications for the health workforce. *Int Health*. Jul 1 2020;12(4):241-245. Doi: 10.1093/inthealth/ihaa007
11. Warning A, Weber E, Puffel A. On the Impact of Digitalization and Artificial Intelligence on Employers' Flexibility Requirements in Occupations-Empirical Evidence for Germany. *Front Artif Intell*. 2022;5:868789. Doi: 10.3389/frai.2022.868789
12. Steimers A, Schneider M. Sources of Risk of AI Systems. *Int J Environ Res Public Health*. 2022;19(6). Doi: 10.3390/ijerph19063641
13. Moshawrab M, Adda M, Bouzouane A, Ibrahim H, Raad A. Smart Wearables for the Detection of Occupational Physical Fatigue: A Literature Review. *Sensors (Basel)*. Oct 2 2022;22(19). Doi: 10.3390/s22197472
14. Mondal S, Zehra N, Choudhury A, Iyer PK. Wearable Sensing Devices for Point of Care Diagnostics. *ACS Appl Bio Mater*. 2021;4(1):47-70. Doi: 10.1021/acsabm.0c00798
15. Kimball JP, Inan OT, Convertino VA, Cardin S, Sawka MN. Wearable Sensors and Machine Learning for Hypovolemia Problems in Occupational, Military and Sports Medicine: Physiological Basis, Hardware and Algorithms. *Sensors (Basel)*. 2022;22(2). Doi: 10.3390/s22020442
16. Podgorski D, Majchrzycka K, Dabrowska A, Gralewicz G, Okrasa M. Towards a conceptual framework of OSH risk management in smart working environments based on smart PPE, ambient intelligence and the Internet of Things technologies. *Int J Occup Saf Ergon*. 2017;23(1): 1-20. Doi: 10.1080/10803548.2016.1214431
17. Huang Y, Benford S, Price D, et al. Using Internet of Things to Reduce Office Workers' Sedentary Behavior: Intervention Development Applying the Behavior Change Wheel and Human-Centered Design Approach. *JMIR Mhealth Uhealth*. 2020;8(7):e17914. Doi: 10.2196/17914
18. Font O, Torrents-Barrena J, Royo D, et al. Validation of an autonomous artificial intelligence-based diagnostic system for holistic maculopathy screening in a routine occupational health checkup context. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(10):3255-3265. Doi: 10.1007/s00417-022-05653-2
19. Ahmed A, Aziz S, Abd-Alrazaq A, Farooq F, Househ M, Sheikh J. The Effectiveness of Wearable Devices Using Artificial Intelligence for Blood Glucose Level Forecasting or Prediction: Systematic Review. *J Med Internet Res*. Mar 14 2023;25:e40259. Doi: 10.2196/40259
20. Ahmed A, Aziz S, Abd-Alrazaq A, Farooq F, Sheikh J. Overview of Artificial Intelligence-Driven Wearable Devices for Diabetes: Scoping Review. *J Med Internet Res*. 2022;24(8):e36010. Doi: 10.2196/36010
21. Beach C, Casson AJ. Impact of shift working on the potential for self-powering via kinetic energy harvesting in wearable devices. *Annu Int Conf IEEE Eng Med Biol Soc*. 2021;2021:7003-7006. Doi: 10.1109/EMBC46164.2021.9631066
22. Campero-Jurado I, Marquez-Sanchez S, Quintanar-Gomez J, Rodriguez S, Corchado JM. Smart Helmet 5.0 for Industrial Internet of Things Using Artificial Intelligence. *Sensors (Basel)*. Nov 1 2020;20(21). Doi:10.3390/s20216241
23. Greenfield R, Busink E, Wong CP, et al. Truck drivers' perceptions on wearable devices and health promotion: a qualitative study. *BMC Public Health*. Jul 30 2016;16:677. Doi: 10.1186/s12889-016-3323-3
24. Kim Y, Choi Y. Smart Helmet-Based Proximity Warning System to Improve Occupational Safety on the Road Using Image Sensor and Artificial Intelligence. *Int J Environ Res Public Health*. Dec 6 2022;19(23). Doi: 10.3390/ijerph192316312
25. Bhat G, Tran N, Shill H, Ogras UY. w-HAR: An Activity Recognition Dataset and Framework Using Low-Power Wearable Devices. *Sensors (Basel)*. 2020;20(18). Doi: 10.3390/s20185356
26. Fukumura YE, Gray JM, Lucas GM, Becerik-Gerber B, Roll SC. Worker Perspectives on Incorporating Artificial Intelligence into Office Workspaces: Implications for the Future of Office Work. *Int J Environ Res Public Health*. 2021;18(4). Doi: 10.3390/ijerph18041690
27. Devagiri VM, Boeva V, Abghari S, Basiri F, Lavesson N. Multi-View Data Analysis Techniques for Monitoring Smart Building Systems. *Sensors (Basel)*. 2021;21(20). Doi: 10.3390/s21206775
28. Yun J, Won KH. Building environment analysis based on temperature and humidity for smart energy systems.

Sensors (Basel). 2012;12(10):13458-70. Doi: 10.3390/s121013458
29. Khairuddin MZF, Lu Hui P, Hasikin K, et al. Occupational Injury Risk Mitigation: Machine Learning Approach and Feature Optimization for Smart Workplace Surveillance. *Int J Environ Res Public Health*. 2022;19(21). Doi: 10.3390/ijerph192113962
30. Kang SY, Min S, Kim WS, Won JH, Kang YJ, Kim S. Types and Characteristics of Fatal Accidents Caused by Multiple Processes in a Workplace: Based on Actual Cases in South Korea. *Int J Environ Res Public Health*. 2022;19(4). Doi: 10.3390/ijerph19042047
31. Khashaba E, El-Helaly M, El-Gilany AH, Motawei SM, Foda S. Risk factors for non-fatal occupational injuries among construction workers: A case-control study. *Toxicol Ind Health*. 2018;34(2):83-90. Doi: 10.1177/0748233717733853
32. Johnston KL, Phillips ML, Esmen NA, Hall TA. Evaluation of an artificial intelligence program for estimating occupational exposures. *Ann Occup Hyg*. 2005;49(2):147-53. Doi: 10.1093/annhyg/meh072
33. Aram SA, Saalidong BM, Appiah A, Utip IB. Occupational health and safety in mining: Predictive probabilities of Personal Protective Equipment (PPE) use among artisanal goldminers in Ghana. *PLoS One*. 2021;16(9):e0257772. Doi: 10.1371/journal.pone.0257772
34. Lee JY, Park J, Park H, et al. What do firefighters desire from the next generation of personal protective equipment? Outcomes from an international survey. *Ind Health*. 2015;53(5):434-44. Doi: 10.2486/indhealth.2015-0033
35. Marchal P, Baudoin J. Proposal for a method for analysing smart personal protective systems. *Int J Occup Saf Ergon*. 2022;28(3):1566-1576. Doi: 10.1080/10803548.2021.1935541
36. Tao H, Rahman MA, Al-Saffar A, et al. Security robot for the prevention of workplace violence using the Nonlinear Adaptive Heuristic Mathematical Model. *Work*. 2021;68(3):853-861. Doi: 10.3233/WOR-203419
37. Byon HD, Harris C, Crandall M, Song J, Topaz M. Identifying Type II workplace violence from clinical notes using natural language processing. *Workplace Health Saf*. 2023;71(10):484-490. Doi: 10.1177/21650799231176078
38. Swaminathan A, Lopez I, Mar RAG, et al. Natural language processing system for rapid detection and intervention of mental health crisis chat messages. *NPJ Digit Med*. 2023;6(1):213. Doi: 10.1038/s41746-023-00951-3
39. Banda JM, Seneviratne M, Hernandez-Boussard T, Shah NH. Advances in Electronic Phenotyping: From Rule-Based Definitions to Machine Learning Models. *Annu Rev Biomed Data Sci*. 2018;1:53-68. Doi: 10.1146/annurev-biodatasci-080917-013315
40. Kumar PM, Pandey HM, Srivastava G. Special Issue on Workplace Violence Prevention using Security Robots. *Work*. 2021;68(3):821-823. Doi: 10.3233/WOR-203415
41. Goplerud E, Hodge S, Benham T. A Substance Use Cost Calculator for US Employers With an Emphasis on Prescription Pain Medication Misuse. *J Occup Environ Med*. 2017;59(11):1063-1071. Doi: 10.1097/JOM.0000000000001157
42. McAndrew KG, McAndrew SJ. Workplace substance abuse impairment: the occupational health care provider's role. *AAOHN J*. 2000;48(1):32-45; quiz 46-7.
43. Barenholtz E, Fitzgerald ND, Hahn WE. Machine-learning approaches to substance-abuse research: emerging trends and their implications. *Curr Opin Psychiatry*. 2020;33(4):334-342. Doi: 10.1097/YCO.0000000000000611
44. Islam A, Khan KM, Scarbrough A, et al. An Artificial Intelligence-Based Smartphone App for Assessing the Risk of Opioid Misuse in Working Populations Using Synthetic Data: Pilot Development Study. *JMIR Form Res*. 2023;7:e45434. Doi: 10.2196/45434
45. Huang Y, Benford S, Li B, Price D, Blake H. Feasibility and Acceptability of an Internet of Things-Enabled Sedentary Behavior Intervention: Mixed Methods Study. *J Med Internet Res*. 2023;25:e43502. Doi: 10.2196/43502
46. Andersen LL, Thorsen SV, Flyvholm MA, Holtermann A. Long-term sickness absence from combined factors related to physical work demands: prospective cohort study. *Eur J Public Health*. 2018;28(5):824-829. Doi: 10.1093/eurpub/cky073
47. El-Helaly M, Balkhy HH, Vallenius L. Carpal tunnel syndrome among laboratory technicians in relation to personal and ergonomic factors at work. *J Occup Health*. 2017;59(6):513-520. Doi: 10.1539/joh.16-0279-OA
48. Mansoor SN, Al Arabia DH, Rathore FA. Ergonomics and musculoskeletal disorders among health care professionals: Prevention is better than cure. *J Pak Med Assoc*. 2022;72(6):1243-1245. Doi: 10.47391/JPMA.22-76
49. El-Helaly M, Elsherbeny E, Haji A, Assiri M, Fadlelmula A. Reported musculoskeletal symptoms among laboratory workers, in relation to individual and work-related physical factors. *Egy J Occup Med*. 2018;42:79-92. Doi: 10.21608/ejom.2018.4940
50. Hulshof CTJ, Pega F, Neupane S, et al. The prevalence of occupational exposure to ergonomic risk factors: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. *Environ Int*. 2021;146:106157. Doi: 10.1016/j.envint.2020.106157
51. Anan T, Kajiki S, Oka H, et al. Effects of an Artificial Intelligence-Assisted Health Program on Workers With Neck/Shoulder Pain/Stiffness and Low Back Pain: Randomized Controlled Trial. *JMIR Mhealth Uhealth*. Sep 24 2021;9(9):e27535. Doi: 10.2196/27535
52. Donisi L, Cesarelli G, Pisani N, Ponsiglione AM, Ricciardi C, Capodaglio E. Wearable Sensors and Artificial Intelligence for Physical Ergonomics: A Systematic

Review of Literature. *Diagnostics (Basel)*. 2022;12(12). Doi: 10.3390/diagnostics12123048
53. Homayounfar SZ, Andrew TL. Wearable Sensors for Monitoring Human Motion: A Review on Mechanisms, Materials, and Challenges. *SLAS Technol*. 2020;25(1): 9-24. Doi: 10.1177/2472630319891128
54. Tsai YL, Wadgaonkar C, Chun B, Knight H. How Service Robots Can Improve Workplace Experience: Camaraderie, Customization, and Humans-in-the-Loop. *Int J Soc Robot*. 2022;14(7):1605-1624. Doi: 10.1007/s12369-022-00898-7
55. Lopes SL, Ferreira AI, Prada R. The Use of Robots in the Workplace: Conclusions from a Health Promoting Intervention Using Social Robots. *Int J Soc Robot*. 2023:1-13. Doi: 10.1007/s12369-023-01000-5
56. Coghlan S. Robots and the Possibility of Humanistic Care. *Int J Soc Robot*. 2022;14(10):2095-2108. Doi: 10.1007/s12369-021-00804-7
57. Payne TH. Computer decision support systems. *Chest*. Aug 2000;118(2 Suppl):47S-52S. Doi: 10.1378/chest.118.2_suppl.47s
58. Nimri R, Piper M, Pinsker JE, Dassau E. Decision Support Systems and Closed Loop. *Diabetes Technol Ther*. Feb 2020;22(S1):S47-S62. Doi: 10.1089/dia.2020.2504
59. Sharma M, Savage C, Nair M, Larsson I, Svedberg P, Nygren JM. Artificial Intelligence Applications in Health Care Practice: Scoping Review. *J Med Internet Res*. 2022;24(10):e40238. Doi: 10.2196/40238
60. Khan B, Fatima H, Qureshi A, et al. Drawbacks of Artificial Intelligence and Their Potential Solutions in the Healthcare Sector. *Biomed Mater Devices*. 2023:1-8. Doi: 10.1007/s44174-023-00063-2
61. Saheb T. "Ethically contentious aspects of artificial intelligence surveillance: a social science perspective". *AI Ethics*. 2023;3(2):369-379. Doi: 10.1007/s43681-022-00196-y
62. Fisher E, Flynn MA, Pratap P, Vietas JA. Occupational Safety and Health Equity Impacts of Artificial Intelligence: A Scoping Review. *Int J Environ Res Public Health*. 2023;20(13). Doi: 10.3390/ijerph20136221
63. Holm JR, Lorenz E. The impact of artificial intelligence on skills at work in Denmark. *New Technology, Work & Employment*. 2022;37(1):79-101.
64. Chen N, Li Z, Tang B. Can digital skill protect against job displacement risk caused by artificial intelligence? Empirical evidence from 701 detailed occupations. *PLoS One*. 2022;17(11):e0277280. Doi: 10.1371/journal.pone.0277280
65. Doki S, Sasahara S, Hori D, et al. Comparison of predicted psychological distress among workers between artificial intelligence and psychiatrists: a cross-sectional study in Tsukuba Science City, Japan. *BMJ Open*. Jun 23 2021;11(6):e046265. Doi: 10.1136/bmjopen-2020-046265
66. Ghani B, Memon KR, Han H, Ariza-Montes A, Arjona-Fuentes JM. Work stress, technological changes, and job insecurity in the retail organization context. *Front Psychol*. 2022;13:918065. Doi: 10.3389/fpsyg.2022.918065
67. Yang S, Liu K, Gai J, He X. Transformation to Industrial Artificial Intelligence and Workers' Mental Health: Evidence From China. *Front Public Health*. 2022;10:881827. Doi: 10.3389/fpubh.2022.881827

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Regulatory and Ethical Considerations on Artificial Intelligence for Occupational Medicine

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Summary

Generative artificial intelligence and Large Language Models reshape labor dynamics and occupational health practices. As AI continues to evolve, there's a critical need to customize ethical considerations for its specific impacts on occupational health. Recognizing potential ethical challenges and dilemmas, stakeholders and physicians are urged to proactively adjust the practice of Occupational Medicine in response to shifting ethical paradigms. By advocating for a comprehensive review of the International Commission on Occupational Health ICOH Code of Ethics, we can ensure responsible medical AI deployment, safeguarding the well-being of workers amidst the transformative effects of automation in healthcare.

1. Introduction

Picking up the legacy of Alan Turing, who in 1950 asked himself the question, "can machines think?" proposing the test named after him and first coined in 1956 at the Dartmouth Summer Research Project on Artificial Intelligence, a seminal event for artificial intelligence as a field where a group of scientists set out to teach machines to use language, form concepts, self-improve, and solve problems originally reserved for humans [1, 2], Artificial Intelligence (AI) is a field of computer science aimed at creating algorithms and systems capable of mimicking human cognitive functions [3, 4].

After several drafts and revisions, the European Parliament approved the final text of the AI Act* on 13 March 2024, becoming the first in the world to try to give clear rules and bans on the development of one of the most disruptive and revolutionary technologies. All artificial intelligence applications and systems operating in the European Union will be classified according to four risk levels (minimal, limited, high, and unacceptable) to protect EU citizens based on the Treaty on European Union (TEU) and the Treaty on the Functioning of the European Union (TFEU).

Integrating digital technology, including AI, is revolutionizing the occupational landscape, redefining the types of available jobs and how work is organized and managed. This change is unstoppable and involves all productive sectors. Some of the most recognizable and prevalent instances of artificial intelligence in occupational settings include human resource (HR) software tools, collaborative robots (cobots) utilized in industrial settings, virtual assistants in customer service centers, wearable devices utilized for real-time training and digital

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platforms facilitating freelance or "gig" employment opportunities [5, 6].

AI-based HR systems are used, for example, for task assignment, performance evaluations, and activity monitoring, such as the technique of people analytics, defined as the use by human resources of data on behavior, relationships, and human traits to make business decisions [7].

Smart personal protective equipments (PPE) are traditional protection systems combined with electronic components (such as sensors that can be incorporated into helmets or safety glasses and mobile or fixed systems via cameras) capable of continuously recording data on the worker, the work environment and the use of the device itself. They allow, for example, the verification of a person on the ground, mapping of hazardous areas, immediate alert of the release of substances hazardous to workers' health but also allergens, noise, and chemicals, or to monitor stress, physical fatigue or to record vital parameters such as core body temperature and heart rate [8-11].

Chatbots represent a model of human-computer interaction and are designed to simulate human conversation, especially via text or voice, using artificial intelligence algorithms. They can be integrated into various platforms, such as websites, instant messaging apps, social media, and email. They can be designed to perform different roles, from customer support services to virtual tutors or conversation companions. In the world of work, they are increasingly used for various purposes. Some chatbots analyze workers' communication patterns to assess the risk of mental health problems, such as burnout, and they can also provide personalized support to workers, such as personalized mindfulness practices through ad hoc platforms like MindBot, an EU-funded project [12]. They are also used to provide information on safety procedures to workers at any time or to manage customer assistance requests, freeing humans working in call centers. Virtual reality is used to train workers towards safer and healthier behaviors. Additionally, cobots or collaborative robots are employed to assist workers and improve efficiency and safety in the workplace across a variety of sectors and applications, such as assembly, logistics, healthcare, agriculture, and more [13, 14], allowing people to be removed from dangerous physical work and environments with chemical and ergonomic hazards, even if they can pose safety issues [15].

Another example of technological integration occurs in the Gig Economy, where digital platforms offer an ecosystem benefiting both workers, known as gig workers (e.g., couriers), and clients or companies. According to 2021 data from the EU Science Hub [16, 17], gig workers represent a rapidly growing workforce, with millions of people employed in the European sector.

From these examples of existing workplace applications, it is confirmed that emerging technologies such as artificial intelligence, automation, the Internet of Things (IoT), including healthcare IOT, robotics, and blockchain, are radically transforming how organizations operate and manage their activities [18], meeting the definition of AI-based worker management (AIWM) technologies.

Data Mining (DM), based on the analysis of Big Data – a subset of Data Science - through Deep Learning (DL) – a subset of ANNs with multi-layer (deep) structures within Machine Learning (ML) - can help researchers in the process of Knowledge Discovery in Databases (KDD) [19-21].

The implementation of increasingly complex technological models, also based on AI, will be able to facilitate the transition to a 5p Occupational Medicine (personalized, preventive, predictive, participatory precision medicine) as would seem possible from the study of digital twin, digital replica that mirrors the physical entity in real-time or near-real-time, enabling simulations and predictive analytics, allowing users to forecast performance, behavior, and potential issues before they occur in the physical world, which could be implemented in Occupational Medicine for the study and prediction of the pathogenesis mechanisms of technopathy providing a deeper understanding of the physical world and enabling data-driven based evidence [19, 22, 23].

In recent years, generative artificial intelligence (GAI), which evolved from Machine Learning (ML), has undergone rapid development. This branch of AI consists of algorithms that learn from large amounts of data to create new content in various formats, such as text, images, video, audio, and

code. These models are known for their ability to perform a wide range of tasks, including writing, poetic composition, literature review, translation, and text adaptation to different contexts [24], simulating human cognitive processes, even if there is no specific correlation between the computer states and cognitive states of the brain. There are large language models (LLMs) within the realm of generative AI. These systems are based on a complex of artificial neural networks (ANNs) capable of mimicking the brain structure and handling vast volumes of written information. They can be employed in various contexts, such as automatic translation, text creation, and question answering [25], generating human-like text. LLMs have rapidly spread globally in the last year and a half and have immediately demonstrated their potential to revolutionize the global medical sector [26]. The potential applications of LLMs in the medical field mainly concern medical education, scientific research, medical clinical practice, and the doctor-patient relationship [27]. The use of chatbots like ChatGPT, based on Generative Pretrained Transformer (GPT), a specific type of LLM developed by OpenAI [28], trained on vast amounts of text data also represents an opportunity in Occupational Medicine because of their capacity to generate coherent, contextually relevant sentences. Unlike traditional chatbots, which are often designed to perform specific tasks or respond to predefined questions, models like ChatGPT are better suited for generating fluid and natural language responses across a wide range of conversational contexts without the need to be programmed or trained on specific data [29].

GAI systems and subsets could be employed as virtual assistants for Occupational Medicine professionals, providing instant responses regarding current health and safety regulations in the workplace [30, 31]. They could also be used to draft informative documents and company communications and write and review risk assessment documentation to fulfill employer regulatory obligations. Finally, they could be employed to develop more efficient management systems for health surveillance, ensuring more comprehensive data collection.

However, it's essential to recognize that the integration of AI and machine learning in healthcare also presents challenges, including concerns about data privacy and security, the need for robust regulatory frameworks, and ensuring that these technologies are accessible and fair for all patients, as highlighted by the EU-OSHA's Healthy Workplaces Campaign Safe and Healthy Work in the Digital Age, running from 2023 to 2025. At the top there are LLM hallucinations, a term result of an anthropomorphization of AI lexicon and currently used when generative AI systems based on Large Language Models (LLM) connect, misinterpret data and produce erroneous information that appears coherent and plausible but lacks factual accuracy or medical validity [32]. This phenomenon poses a significant problem for medical applications because healthcare professionals might encounter AI-generated content that looks accurate but could lead to incorrect diagnoses or treatments if relied upon without scrutiny because of the so-called counterfactual bias or the tendency to consider an incorrect factual premise true. The causes of LLM hallucinations can be varied and complex. One of the main reasons is the sensitivity of LLMs to training data or the presence of patterns that can mislead the algorithm. Ambiguous or non-representative data can generate erroneous responses that reflect distorted interpretations of reality with significant ethical and safety implications. These are errors that are sometimes so gross that they are immediately obvious. However, continued progress in LLM training (e.g., human feedback) will constantly reduce gross hallucinations to form more reliable generative models. However, regardless of whether issues of hallucinations are adequately addressed, healthcare providers should be aware of the spectrum of capabilities and limitations of generative AIs, ensuring that medical decisions are based on reliable evidence and professional knowledge rather than solely relying on AI-generated text that may not always be accurate or clinically appropriate. Cautious use and careful fact-checking are crucial, alongside transparency, surveillance, and regulation, as already warned [33-35].

Therefore, careful consideration and ongoing evaluation are necessary to harness AI's full potential in improving healthcare services while effectively addressing these challenges [36].

2. Discussion

The risks arising from digitization in the workplace fall within the scope of Council Directive 89/391/EEC [32], the framework directive on occupational health and safety, and the national legislation that has implemented it. In addition to protecting workers from work-related risks, it also establishes the employer's responsibility to ensure safety and health in the workplace. The main risks arising from technological integration include loss of awareness of events, excessive reliance or potential loss of specific job-related skills, demotion, loss of autonomy and employment, social isolation, privacy violations, and inability to draw clear boundaries between social and private life due to 24/7 access to technologies [5].

Even gig workers, while enjoying a certain autonomy typical of freelance workers, are subject to a high degree of control over their activities by digital platforms they work for through management algorithms. During the COVID-19 health emergency, the European Commission recognized gig workers as essential workers, emphasizing the crucial role they play in ensuring the continuous functioning of vital services for public safety and health [38]. However, the ambiguous nature of their employment status has made it complex to classify them legally and protect their rights, particularly concerning health and safety at work.

In August 2023, the ILO published a working paper entitled 'Generative AI and Jobs: A Global Analysis of Potential Effects on Job Quantity and Quality', which presents a comprehensive analysis of the potential exposure of occupations and tasks to Generative Artificial Intelligence, specifically LLMs based on Generative Pre-Trained Transformers (GPTs), and the possible implications of such exposure for job quantity and quality. Unlike previous waves of technological transformation that primarily affected low-skill and repetitive jobs with the highest potential for automation, machine learning systems can enhance performance in non-routine tasks. The proliferation of GPT-based LLMs further underscores this evolving trend, given their capacity to execute cognitive tasks such as analyzing text, drafting documents and messages, or scraping private repositories and the web for additional information. Consequently, this new wave of automation will primarily target a different group of workers, typically associated with 'knowledge work,' including clerical jobs. The anticipated impact appears to be not the obliteration of jobs but rather potential changes in the quality of jobs, particularly regarding work intensity and autonomy. The socio-economic impacts of Generative Artificial Intelligence are not predetermined; rather, they will largely depend on how its deployment is managed, necessitating policies that support an orderly, equitable, and consultative transition [39].

Psychosocial risks may worsen with the spread of generative AI and LLM in the workplace, or new risks may arise. At present, there are no official sources that deal with the use of AI in Occupational Medicine. Only recently, the World Health Organization (WHO) issued two documents related to AI [40] and LLMs and Generative AI [41]. At the same time, the International Code of Ethics for Occupational Health Professionals, last updated in 2014, contains neither recommendations nor guidelines on using AI.

WHO documents offer safety recommendations for the usage of AI in healthcare, covering six key areas: documentation and transparency, total product lifecycle and risk management, intended use and validation, data quality, privacy and data protection, and engagement and collaboration. They also integrate their previous 2021 publication [42], as the latter didn't consider the potential applications of LLMs as they were not as advanced yet, by providing more than 40 recommendations. Its goal is to ensure the appropriate use of LMMs to protect public health, emphasizing the need to carefully consider the risks associated with developing and using generative AI technologies to improve healthcare.

The WHO identifies five areas of application of LMMs in healthcare: clinical diagnosis, patient-guided care, administrative tasks, medical training, and scientific research for drug development. The same guidelines outline ethical considerations and best practices for developing, implementing, and responsibly using these models. WHO highlights the need to consider crucial aspects such as privacy, data

security, transparency, accountability, and fairness when using these technologies. Based on what has recently been published by the WHO, we believe that the rapid progress of artificial intelligence in the medical field must also be considered in Occupational Medicine to analyze its possible uses and ensure its correct application. Occupational physicians should consider the impact of AI and, in particular, of LLMs from two perspectives:

- The impact that generative AI may have in terms of employment and organizational well-being. Its introduction may cause new work hazards due to the possible workers' demotion, burnout, and alienation caused by employers' increasing adoption of AI. This is also underscored by the WHO guidelines, where the potential loss of jobs and the need for workers to reinvent themselves and adapt to AI-enabled jobs were inserted among the risks for the healthcare systems.
- The impact of generative AI on occupational physicians' daily practice. For example, the use of LLMs on patients' private data may pose ethical and privacy concerns about how user data is handled and stored when submitted to third-party systems. Also, LLM hallucinations may lead to wrong diagnoses if used unchecked by the health professional.

To raise awareness of Generative AI opportunities and potential downfall and regulate its utilization in the medical fields, we believe that the WHO guidelines should be incorporated into the ethical codes in force in Occupational Medicine like the International Code of Ethics published by the International Commission on Occupational Health (ICOH)[43, 44].

Several key considerations deserve integration into the ICOH Code of Ethics:

- Transparency and explainability. The code should underscore, reiterate, and enforce the necessity of transparency among workers concerning clinical decision-making supported by LLMs, with occupational health professionals being the first responsible for the transparent utilization of such technologies.
- Human oversight and accountability. In a landscape where LLMs wield substantial influence over clinical decisions, elucidating the responsibilities of occupational health practitioners and other professionals in generative AI usage is imperative.
- Data privacy and confidentiality. Privacy concerns must be reaffirmed within the code, emphasizing the confidentiality of health surveillance data processed through LLMs.
- Equity and bias. Given the potential for LLMs to reflect and amplify biases, the code should stress the importance of mitigating discrimination risks and promoting equitable access to and utilization of these technologies, particularly in health surveillance and clinical decision-making.
- Ethical use and learning. Continuous education and professional development are essential. Occupational health practitioners should undergo appropriate training in the ethical and responsible use of LLMs and engage in ongoing professional development to stay abreast of technological advancements and emerging ethical dilemmas.
- Continuous Monitoring and updating. The code should advocate for continuous monitoring and evaluation of the ethical implications and effectiveness of LLMs utilization in clinical practice and Occupational Medicine research, focusing on identifying and rectifying any issues or challenges that may arise.

Updating the ICOH code of ethics in Occupational Medicine in light of the WHO guidelines would help ensure that using LLMs in this field is ethical and respects workers' rights.

As pointed out in the preface of the publication "The International Code of Ethics for Occupational Health Professionals" by the Italian National Institute for Insurance against Accidents at Work (INAIL) [45], the Code represents a starting point and not an arrival point in a dynamic process involving the entire occupational health community. Therefore, the development and application of professional standards according to a multidisciplinary approach that remains in step with the times should

express itself, along the lines of the WHO, on the new ethical challenges and the governance of generative AI given the possible applications of LLMs in Occupational Medicine and in general in the international occupational health landscape.

The Italian Society of Occupational Medicine (SIML) could later adopt the updated code of ethics. This could pave the way for drafting national guidelines for using GAI and LLMs in Occupational Medicine.

3. Conclusion

Artificial Intelligence (AI) has the potential to revolutionize Occupational Medicine by improving efficiency, accuracy, and personalized healthcare for workers. However, addressing challenges such as data privacy, ethics, and integration is crucial for successful implementation.

Updating the ICOH Code of Ethics in Occupational Medicine, considering recent developments in Generative AI, could help maximize workers' health and safety benefits while embracing this technological revolution. On the other hand, it would also enable the containment of associated ethical and clinical risks arising from using LLMs by occupational physicians. Moreover, alongside integrating the code of ethics, the definition of specific Occupational Medicine guidelines for using LLM in Occupational Medicine could be a starting point for new generations of young occupational physicians entering this field. The discipline of Occupational Medicine cannot afford to remain stagnant in the face of the scientific world's embrace of Generative AI. In this rapid technological evolution, it is crucial to set clear ethical and governance limits and promote open-mindedness among all occupational health and safety protection professionals. Integrating these innovations into the workplace and the clinical practice of occupational physicians intelligently and responsibly is a challenge we must all undertake. The future will not see artificial intelligence replace the occupational physician but, possibly, the occupational physician who will be able to use, according to scrutiny and criticism, artificial intelligence as a further step forward in the health and safety of workers.

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References

1. A. M. TURING, I.—COMPUTING MACHINERY AND INTELLIGENCE, Mind, Volume LIX, Issue 236, October 1950, Pages 433–460, https://doi.org/10.1093/mind/LIX.236.433
2. McCarthy J, Minsky ML, Rochester N, Shannon C E (2006). A Proposal for the Dartmouth Summer Research Project on Artificial Intelligence, August 31, 1955. *AI Magazine*. 27(4): 12. Doi: https://doi.org/10.1609/aimag.v27i4.1904
3. Haug, Charlotte J, Drazen JM. Artificial Intelligence and Machine Learning in Clinical Medicine, 2023. *New Eng J Med* vol. 388;13(2023):1201-1208. Doi: 10.1056/NEJMra2302038)
4. Bhattad PB, Jain V. Artificial Intelligence in Modern Medicine – The Evolving Necessity of the Present and Role in Transforming the Future of Medical Care. *Cureus*. Published online 2020. Doi: 10.7759/cureus.8041
5. Leso V, Fontana L, Iavicoli I. The occupational health and safety dimension of Industry 4.0. *Med Lav.* 2018 Oct 29;110(5):327-338. Doi: 10.23749/mdl.v110i5.7282. PMID: 30378585; PMCID: PMC7682172
6. EU-OSHA (European Agency for Safety and Health at Work), 2019,OSH and the Future of Work: benefits and risks of artificial intelligence tools in (Available online: https://osha.europa.eu/en/publications/osh-and-future-work-benefits-and-risks-artificial-intelligence-tools-workplaces, accessed 05 February 2024)
7. Collins L, Fineman DR, Tsuchida A. 2017. People Analytics: Recalculating the Route. In Walsch, L. and Volini, E.'s Rewriting the rules for digital age. Deloitte University press. 97-106 (Available online: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/About-Deloitte/central-europe/ce-global-human-capital-trends.pdf, accessed 15 February 2024)

8. Mokhtari F, Cheng Z, Wang CH, Foroughi J. Advances in Wearable Piezoelectric Sensors for Hazardous Workplace Environments. *Global Challenges*. 2023;7(6). Doi: 10.1002/gch2.202300019
9. Baldassarre A, Mucci N, Padovan M, et al. The role of electrocardiography in Occupational Medicine, from Einthoven's invention to the digital era of wearable devices. *Int J Environ Res Public Health*. 2020;17(14). Doi: 10.3390/ijerph17144975
10. Prince SA, Elliott CG, Scott K, Visintini S, Reed JL. Device-measured physical activity, sedentary behaviour and cardiometabolic health and fitness across occupational groups: A systematic review and meta- analysis. *International Journal of Behavioral Nutrition and Physical Activity*. 2019;16(1). Doi: 10.1186/s12966-019-0790-9
11. Piwek L, Ellis DA, Andrews S, Joinson A. The Rise of Consumer Health Wearables: Promises and Barriers. *PLoS Med*. 2016;13(2). Doi: 10.1371/journal.pmed.1001953
12. Horizon 2020 Mental Health promotion of cobot Workers in Industry 4.0 https://cordis.europa.eu/project/id/847926, Doi: 10.3030/847926 [Last Accessed 06-02-2024].
13. Murashov V, Hearl F, Howard J. Working safely with robot workers: Recommendations for the new workplace. *J Occup Environ Hyg.* 2016;13(3). Doi: 10.1080/15459624.2015.1116700
14. Paliga M. The Relationships of Human-Cobot Interaction Fluency with Job Performance and Job Satisfaction among Cobot Operators—The Moderating Role of Workload. *Int J Environ Res Public Health.* 2023;20(6). Doi: 10.3390/ijerph20065111
15. EU-OSHA (European Agency for Safety and Health at Work), 2018. "Foresight on new and emerging occupational safety and health risks associated with digitalisation by 2025" European Risk Observatory Report. (Available online: https://osha.europa.eu/en/publications/foresight-new-and-emerging-occupational-safety-and-health-risks-associated) [Last Accessed 20-02-2024].
16. Berg J, Hilal A, El S, Horne R. (2021). World employment and social outlook: Trends 2021. International Labour Organization.
17. Wu D, Huang JL. Gig work and gig workers: An integrative review and agenda for future research. *J Organizat Behav*.2024;45(2):183–208. Doi: https://doi.org/10.1002/job.2775
18. Adel, A. Future of industry 5.0 in society: human-centric solutions, challenges and prospective research areas. *J Cloud Comp.* 2022;11:40. Doi: https://doi.org/10.1186/s13677-022-00314-5
19. Topol Review (2019) Preparing the healthcare workforce to deliver the digital future. Final Report February 2019 – A Call For Evidence. A Middleton invited to contribute. Health Education England. (Available online: https://topol.hee.nhs.uk)
20. Boffetta P, Collatuzzo G. Application of P4 (Predictive, Preventive, Personalized, Participatory) Approach to Occupational Medicine. *Med Lav.* 2022 Feb 22; 113(1):e2022009. Doi: 10.23749/mdl.v113i1.12622. PMID: 35226650; PMCID: PMC8902745
21. Blobel B, Kalra D. Editorial: Managing healthcare transformation towards P5 medicine. *Front Med* (Lausanne). 2023 Aug 25;10:1244100. Doi: 10.3389/fmed.2023.1244100.PMID:37692783;PMCID:PMC10485846
22. Kamel Boulos MN, Zhang P. Digital Twins: From Personalised Medicine to Precision Public Health. *J Pers Med* 2021; 11(8):745. Doi: https://doi.org/10.3390/jpm11080745
23. Armeni P, Polat I, Maria De Rossi L. (2023). Digital Twins for Health: Opportunities, Barriers and a Path Forward. *IntechOpen*. Doi: 10.5772/intechopen.112490
24. Shoja MM, Van de Ridder JMM, Rajput V. The Emerging Role of Generative Artificial Intelligence in Medical Education, Research, and Practice. *Cureus*. 2023 Jun 24;15(6):e40883. Doi: 10.7759/cureus.40883. PMID: 37492829; PMCID: PMC10363933).
25. Wayne Xin Zhao. A Survey of Large Language Models. *Arxiv*. Doi: 10.48550/arXiv.2303.18223
26. Lee, Peter et al. "Benefits, Limits, and Risks of GPT-4 as an AI Chatbot for Medicine. Reply." *New Eng J Med* vol. 388,25 (2023): 2400. Doi: 10.1056/NEJMc2305286)
27. Thirunavukarasu AJ, Ting DSJ, Elangovan K, Gutierrez L, Tan TF, Ting DSW. Large language models in medicine. *Nat Med.* 2023;29(8). Doi: 10.1038/s41591-023-02448-8).
28. Naveed H, Khan AU, Qiu, S, et al. A Comprehensive Overview of Large Language Models. *arXiv* 2023, arXiv:2307.06435
29. Chakraborty, Chiranjib et al. "Overview of Chatbots with special emphasis on artificial intelligence-enabled ChatGPT in medical science." *Front Artif Intell* vol. 6 1237704. 31 Oct. 2023, Doi: 10.3389/frai.2023.1237704
30. Sridi C, Brigui S. The use of ChatGPT in Occupational Medicine: opportunities and threats. *Ann Occup Environ Med*. 2023;35:e42. Doi: 10.35371/aoem.2023.35.e42. PMID: 38029273; PMCID: PMC10654530)
31. Padovan M, Cosci B, Petillo A, et al. ChatGPT in Occupational Medicine: A Comparative Study with Human Experts. *Bioengineering*. 2024;11(1):57.Doi: https://doi.org/10.3390/bioengineering11010057
32. Ji Z, Lee N, Frieske R, et al. Survey of hallucination in natural language generation. *ACM Comput. Surv*. 2023,55, 1–38.
33. Mutti A. Hey James, Write an Editorial for "La Medicina del Lavoro". *Med Lav.* 2023;114(2):e2023014. Doi: 10.23749/mdl.v114i2.14451. Epub 2023 Apr 13. PMCID: PMC10133773
34. Menz BD, Modi ND, Sorich MJ, Hopkins AM. Health Disinformation Use Case Highlighting the Urgent Need

for Artificial Intelligence Vigilance: Weapons of Mass Disinformation. *JAMA Intern Med.* 2024;184(1):92–96. Doi: 10.1001/jamainternmed.2023.5947
35. EU-OSHA (European Agency for Safety and Health at Work), 2024. Worker management through AI. From technology development to the impacts on workers and their safety and health. Discussion paper. (Available online: https://osha.europa.eu/en/highlights/ai-worker-management-worker-safety-and-health-considered) [Last Accessed 19-03-2024].
36. Meskó B, Topol EJ. The imperative for regulatory oversight of large language models (or generative AI) in healthcare. *NPJ Digit Med.* 2023;6(1). Doi: 10.1038/s41746-023-00873-0)
37. Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work (https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31989L0391) [Last Accessed 6-02-2024].
38. Friedland J, Balkin DB. When gig workers become essential: Leveraging customer moral self-awareness beyond COVID-19. *Bus Horiz.* 2023 Mar-Apr;66(2):181-190. Doi: 10.1016/j.bushor.2022.05.003. Epub 2022 May 15. PMID: 35601275; PMCID: PMC9107384
39. Gmyrek P, Berg J, Bescond D. 2023. Generative AI and jobs: A global analysis of potential effects on job quantity and quality, ILO Working Paper 96 (Geneva, ILO). https://doi.org/10.54394/ FHEM8239
40. Regulatory considerations on artificial intelligence for health. Geneva: World Health Organization; 2023. License: CC BY-NC-SA 3.0 IGO
41. Ethics and governance of artificial intelligence for health. Guidance on large multi-modal models. Geneva: World Health Organization; 2024. License: CC BY-NC-SA 3.0 IGO).
42. Ethics & Governance of Artificial Intelligence for Health". Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240029200, accessed 30 January 2024).
43. International Commission on Occupational Health (ICOH). International code of ethics for occupational health professionals. ICOH, Third edition, 2014
44. The ICOH International Code of Ethics for Occupational Medicine Practitioners: Historical Fortunes and Future Perspectives in Italy. *Med Lav.* 2016;107(6):485-489
45. INAIL. Il codice internazionale di etica per gli operatori di medicina del lavoro. 2016 ISBN-978-88-7484-511-8

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Occupational Risk for Coronary Artery Disease in Shift Workers – A Systematic Review

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Abstract

Background: *Coronary artery disease (CAD) prevention in shift workers (SWs) poses a significant challenge worldwide, as CAD remains a major cause of mortality and disability. In the past, SWs were found at higher risk of CAD than non-s SWs. Nevertheless, the pathogenic mechanism between shift work and CAD to date is unclear. This systematic review aims to enhance understanding of the risk of CAD occurrence in SWs.* **Methods:** *A systematic literature review was conducted from January 2013 to December 2023. MEDLINE/Pubmed databases were used initially, and additional relevant studies were searched from references. Shift work was defined as any schedule outside traditional shifts, including the night shift.* **Results:** *Fifteen pertinent papers were categorized into risk assessment or risk management. Findings demonstrated an increased risk of CAD among SWs compared to non-SWs, with an increased CAD risk observed for both shift work and night shift work.* **Discussion:** *Duration-response associations indicate that greater shift exposure is linked to higher CAD risk. SWs incur an increased risk of CAD through the atherosclerotic process. As shift work duration increases as the risk of atherosclerosis is higher, workers demonstrate a higher prevalence and severity of coronary artery plaques.* **Conclusions:** *The evidence-based results underscore the increased risk of CAD in SWs and are sufficient for proposing guidelines aimed at reducing the risk of CAD in SWs and at managing people with CAD in return to work characterized by disrupted circadian rhythms.*

1. Introduction

Preventing coronary artery disease (CAD) among shift-workers (SWs) presents a significant global challenge for both workers and enterprises worldwide. CAD, a condition where the heart's arteries fail to deliver sufficient oxygen-rich blood, remains a leading cause of disability [1, 2]. To date, CAD persists as a major cause of mortality, responsible for one-third of all deaths in individuals aged ≥ 35, with a global prevalence ranging from 5% to 8% [3, 4]. Low- and middle-income countries bear a disproportionately higher burden of CAD, recording 7 million deaths and 129 million disability-adjusted life years annually. In the United States, CAD affects 16.8 million individuals, resulting in nearly 8 million cases of myocardial infarction (MI) [5, 6].

The World Health Organization (WHO) estimated that CAD will remain one of the top three causes of death worldwide, with nearly 9.3 million

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deaths annually in 2030 [7]. Moreover, the economic impact of CAD is significant, with CAD-associated financial burdens in the U.S. amounting to $188 billion in 2015 and projected to exceed $366 billion by 2035 [8].

A growing body of literature has revealed a relationship between shift work and the disruption of circadian rhythms and alerting cycles, resulting in an increased risk of cardiovascular diseases, including CAD [9-11].

In the past, a prospective cohort study among Japanese workers indicated that rotating SWs had a higher risk of death due to CAD compared to daytime workers [12], aligning with the findings of a British cohort study associating nighttime and early morning work with adverse CAD risk profiles attributable to socio-economic and occupational factors [13]. Moreover, in a systematic review, Bøggild & Knutsson [14] found that SWs had a 40% increase in the risk of cardiovascular diseases, including CAD, and suggested analyzing the risk factors for such diseases, given that the risk is probably multifactorial. Still, the literature was mainly focused on the behavior of SWs and neglected other possible causal connections.

Nevertheless, to date, the pathogenic mechanism between shift work and CAD is unclear. However, circadian rhythm disruption (through changes in the sleep/wake cycle) is known to be associated with an increase in psychosocial stress, a change in eating habits (i.e., eating an overly rich diet at night), and the autonomic nervous system unbalance [15, 16]. In particular, the role of autonomic cardiovascular control in promoting CAD in SWs is complex and only partially understood. Previously, Furlan et al. [17] first described the circadian changes in cardiac autonomic control in shift workers and suggested that the mismatch between the endogenous circadian rhythms and the continuous changes in the time of work and sleep may increase the risk of cardiac diseases. Thus, increasing evidence shows that shift working patterns might be associated with chronic circadian misalignment, resulting in a decrease in leptin and an increase in glucose and insulin. Due to these changes, individuals may experience increased body weight, high blood glucose, impaired glycogenesis, and an increased risk of CAD [18-27].

Interestingly, in a prospective cohort study of retired workers, Li et al. [28] found an association between the duration of past shift work and increased risk of incident CAD, particularly among service or sales workers compared to workers in other job categories. Moreover, being physically active after retirement proved protective in lowering the excess CAD risk associated with past shift work. In such study, incident CAD events were defined as the first occurrence of fatal or nonfatal coronary events as described by the International Classification of Diseases, Tenth Revision, codes I20– I25 [29], following the recommended guidelines for observational research from the American Heart Association [30]. Although several studies in the past proved associations between shift work and CAD, many of such studies suffer from selection bias, which raises the need to study the association between shift work and CAD and to upgrade the understanding of this issue [11]. Moreover, in a recent editorial, Harma et al. [31] highlighted that many studies focusing on SWs have quality problems as they suffer from the "healthy shift worker effect" and, therefore, may not sufficiently add to the knowledge.

Given the current concern with the impact of shift work on workers' health, with increased risk of CAD, a summary of new evidence may help to accelerate or stimulate policymakers to enact guidelines for preventing and screening CAD in SWs. Indeed, shift work is a modifiable risk factor that seems to be associated with an increased risk of cardiac diseases, including CAD, as reported by several previous studies. The present systematic review aimed to search for new additional insights or new occupational interventions produced by the last 10-year period to mitigate the risk of CAD among SWs.

For the purpose of this systematic review, shift work was defined as any work schedule outside traditional shifts, including night shift; CAD was defined as ischemic heart disease (IHD) according to the International Classification of Diseases, 10th revision (ICD-10) codes I20–25, a condition in which there is an inadequate supply of blood and oxygen to the myocardium; it is sometimes called coronary heart disease [2, 29].

2. Materials and Methods

2.1. Search Strategy

We performed a systematic review of the literature starting from January 1, 2013, up to December 31, 2023. Initially, MEDLINE/PubMed databases were used; afterward, the reference sections of the selected publications were scanned for relevant studies satisfying the adopted criteria. Selected keywords were used to identify articles for this systematic review of literature.

The keywords as search MeSH were: "ischemic heart disease," or "coronary heart disease," "coronary artery disease," or "myocardial infarction" and "shift work" or "rotating shift work" or "night shift work" or "irregular work schedule."

We aimed to identify original research articles (i.e., non-reviews) using the above-mentioned keywords with the following inclusion criteria: i) written in English; ii) published after December 31, 2012 and before January 1, 2024; iii) human studies; and iv) full reports.

Eligibility criteria were established using the PICOS reporting system [32]:

- Population: employees from 18 to 70 years old exposed to shift work.
- Intervention: shift work is defined as any work schedule outside traditional shifts, including the night shift.
- Comparator(s): employees working on schedules without shifts.
- Outcome(s): any evaluation of CAD risk in shift workers, with evaluations of occupational interventions aimed at mitigating the risk as a secondary outcome.
- Study type: case-control studies, cross-sectional studies, retrospective and prospective cohort studies, survey studies, case series, and case reports.

2.2. Formulating the Answerable Question

According to the PICO framework, the question of the present study can be summarized as follows: do SWs face an increased risk for CAD than non-SWs?

2.3. Data Extraction

The screening of articles was carried out in two phases. In the first phase, articles were screened based on title and abstract. The abstracts of all the selected titles were sorted for more detailed information. Two independent reviewers (G.d and G.C.) read the abstracts and categorized them as relevant, not relevant, and possibly relevant. In the second phase, the full-text articles were assessed for eligibility. Two reviewers (R.T. and P.P.) independently applied inclusion criteria to potentially eligible papers and both reviewers then independently extracted data from the original articles. Disagreements were discussed and resolved through a consensus session with a third-party researcher (GLT), and a consensus was reached.

2.4. Quality Assessment

The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the studies [33]. 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; 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 to assess the quality of cross-sectional studies appropriately. Through a search of the literature, we found that a NOS score of 7 or more can be considered a "good" study [34]. So, we used this criterion as a cut-off for good quality study.

2.5. Categorization of Selected Articles

Every full-text article that met the inclusion criteria was reviewed and categorized into one or more categories based on its subject matter: risk assessment and risk management. This systematic review

was reported in accordance with the PRISMA statement [35].

2.6. Search for Ongoing Clinical Trials

The Clinical Trials.gov website, the European Union Clinical Trials Register, the International Council for Harmonization Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Clinical Trials Registry, the Australian New Zealand Clinical Trial Registry, the Chinese Clinical Trial Registry, the Thai Clinical Trials Registry, the International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials were consulted online on March 2023 using the selected keywords (last updated on January 31, 2024).

3. Results

Our research of the literature database retrieved 445 publications that matched our inclusion criteria; 421 were removed because they were deemed irrelevant (i.e., non-research conference proceedings or not concerning SWs). Therefore, 15 papers remained in the study (Figure 1). These 15 papers were then categorized according to their subject matter. Fourteen of the checked studies focused on "risk assessment," and only one paper targeted the focus "risk management." The characteristics, outcomes, and main results of the checked studies are reported in Tables 1 and 2.

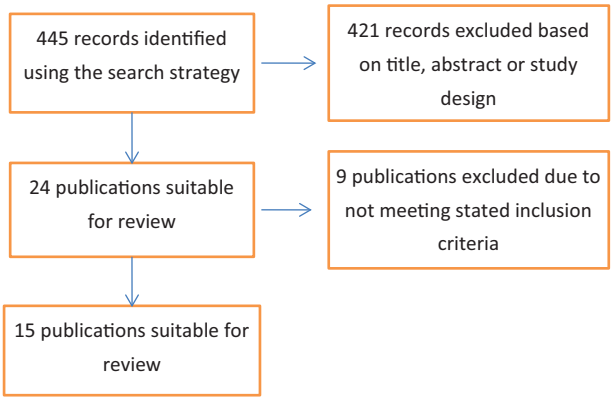

Figure 1. Flow-chart of included studies.

3.1. Best-Evidence Synthesis

The studies were considered good quality if the NOS score was 7 or more. All 14 studies focusing on the risk assessment of CAD reach a good quality level. Eleven had a cohort design, two had a cross-sectional design, and one had a case-control design. The reported odds ratios (ORs), and hazard ratios (HRs) proved moderate evidence for a positive relationship between shift work and CAD; two studies found increased CAD mortality among workers exposed to shift work. The interventional study targeted at risk management of CAD risk reached a level of good quality. It showed the effectiveness of leisure-time physical activity in minimizing the risk of CAD in shift workers (Tables 1, 2).

4. Discussion

The 14 articles focusing on the risk assessment of CAD in shift-workers aimed to identify the relationship between shift work and the occurrence of CAD. In all the reviewed papers, an increased risk of CAD was found among SWs compared to non-SWs after adjusting for covariates, consistent with a meta-analysis of Vyas et al. [23], which previously reported increases in CAD risk of 10%–30% for shift-work and 40% for night shift-work. Moreover, the findings of our search align with those of Torquati et al. [11], who found that shift work was associated with an increased risk of both CAD morbidity and mortality. Interestingly, the cohort study by Jørgensen et al. conducted on the female nurses of the Danish nurse cohort showed an increased rate of CAD mortality (130%) related to night shift work [36]. Studies investigating gender differences in CAD confirmed the slightly higher risk in females than males for either night shifts or shift work in general. In particular, the longitudinal study by Eng et al. [37] found associations between males and females, with higher HRs for CAD observed in females (HR 1.25; 95% CI 1.17 to 1.34) than in males (HR 1.10; 95% CI 1.05 to 1.14). However, despite this evidence, the reviewed studies did not establish the pathway leading to such gender differences in CAD risk.

Table 1. Summary of the articles included in the review.

Reference	Study design	Study location	Sample size	Risk assessment	Risk management	Risk of bias assessment[a)]	Adjustment of covariates	Quality (NOS[b)])
Havakuk et al. (2018) (39)	Cohort	Israel	349	X		Low	Age, gender, hypertension, hyperlipidemia, diabetes mellitus, family history of CAD, smoking status, BMI, physical activity, clinical status	8
Barger et al. (2017) (50)	Cohort	United States	13 026	X		Low	Age, gender, current smoker, race, region, BMI, hypertension, hyperlipidemia, diabetes mellitus, past MI, past percutaneous coronary intervention, index diagnosis (ST-elevation MI versus non-ST-elevation ACS), days from qualifying event, baseline low-density lipoprotein, Lp-PLA2 activity, baseline estimated glomerular filtration rate	8
Mamen et al. (2020) (48)	Interventional	Norway	Intervention = 19 Control group = 37		X	Low	Age, height, BMI, systolic blood pressure, diastolic blood pressure, CRP, total cholesterol, high-density lipoprotein, low-density lipoprotein, glycated hemoglobin, vigorous physical activity, maximal oxygen uptake relative to body mass, maximal oxygen uptake	7
Eng et al. (2022) (37)	Cohort	New Zeland	1.594.677	X		Moderate	Age, gender, ethnicity, smoking status	7
Solymanzadeh et al. (2023) (51)	Cross sectional	Iran	60 shift workers 60 day workers	X		Moderate	Age, gender,BMI, blood pressure, cholesterol	7
Wang et al. (2021) (42)	Cohort	UK	283 657	X		Low	Age, gender, ethnicity, education, socioeconomic status, BMI, smoking status, physical activity, total cholesterol, glycated haemoglobin, blood pressure, sleep duration, chronotype.	7
Carreòn et al. (2014) (52)	Cohort	United States	1874	X		Moderate	Age, gender, smoking status	7

(continued)

Table 1. Summary of the articles included in the review. *(continued)*

Reference	Study design	Study location	Sample size	Risk assessment	Risk management	Risk of bias assessment[a)]	Adjustment of covariates	Quality (NOS[b)])
Kang et al. (2016) (40)	Cross sectional	South Korea	110	X		Moderate	Age, low-density lipoprotein cholesterol, BMI, physical activity, smoking, hypertension, diabetes mellitus	7
Vetter et al. (2016) (45)	Cohort	United States	189.158	X		Low	Medical history, anthropometric data, diet, lifestyle	8
Hermansson et al. (2018) (41)	Case-control	Sweden	Cases 5941 Controls 7252	X		Low	Triglycereds, cholesterol, blood pressure. Diabetes type II, BMI>28, job strain, tobacco smoking	8
Wang et al. (2016) (53)	Cohort	Finland	1891	X		Low	Demographic, biological, behavioural and psychosocial job factors	7
Ho et al. (2021) (38)	Cohort	UK	238.661	X		Low	Sex, age, ethnicity, education level, deprivation index, work h per week, duration of current job, walking/ standing at work, heavy manual/physical work, sleep duration, television viewing, smoking, alcohol intake, blood pressure, low-density lipo-protein, cholesterol, lipoprotein(a), glycated haemoglobin, cystatin C and γ-glutamyltransferase	9
Jørgensen et al. (2017) (36)	Cohort	Denmark	18 015 female nurses	X		Low	Age, smoking status, leisure-time physical activity, alcohol consumption,BMI, pre-existing diseases, work stress, marital status.	8
Kader et al. (2022) (44)	Cohort	Sweden	30.300	X		Low	Gender, age, country of birth, education, and profession.	8
Vestergaard et al. (2023) (47)	Cohort	Denmark	100.149 night workers and 153.882 day workers	X		Moderate	Age, gender, diabetes, family history of cardiovascular disease, educational level, BMI, hypercholesterolaemia, hypertension	8

a) Risk of bias due to: shift work exposure definition, exposure assessment,reliability, confounders assessment, analysis methods in the study (research-specific bias), blinding of assessors, attrition, selective reporting, funding, conflict of interest.

b) Newcastle–Ottawa scale (NOS).

Table 2. Characteristics, outcomes and main results of the checked articles.

Reference	Primary Outcome	Methods	Main results
Havakuk et al. (2018) (39)	To assess the prevalence and the degree of CAD among shift workers, as detected by cardiac computed tomography angiography, compared with non-shift workers	Cardiac computed tomography angiography	CAD was present in 74.2% of shift workers and 53.9% of non-shift workers (OR 2.38, CI 1.21-4.96, p = 0.01), stenosis >50% was more prevalent in shift workers (20.2 vs. 11.2%, respectively; p = 0.006), and a coronary calcium score of zero was shown in 46.8% of shift workers and 63.4% non-shift workers (p = 0.034)
Barger et al. (2017) (50)	To assess predictors of major coronary events	Questionnaire	Patients working overnight shifts for at least 1 year had a 15% increased risk of major coronary events (adj HR, 1.15; 95% CI, 1.03–1.29; P=0.01), a 12% increased risk of major adverse cardiovascular (adj HR, 1.12; 95% CI, 1.00–1.27; P=0.06) and a 21% increased risk of myocardial infarction (adj HR, 1.21; 95% CI, 1.04–1.39; P=0.01) than those who did not report working overnight shifts
Mamen et al. (2020) (48)	To study if high-intensity physical activity could modify the risk of early manifestations of CVD in shift-workers	Questionnaire, examination, laboratory tests	Physical activity could counteract the increased risk for CADin shift-workers
Eng et al. (2022) (37)	To examine associations between occupational exposure to noise, long working h, shift work, sedentary work and ischaemic hearth disease.	Survey	Night shift work was associated with ischaemic hearth disease for males (HR 1.10; 95% CI 1.05 to 1.14) and females (HR 1.25; 95% CI 1.17 to 1.34).
Solymanzadeh et al. (2023) (51)	To determine the prediction of risk of CAD based on the Framingham risk score (FRS) in association with shift work among nurses.	CAD risk assessment tools	Shift-work was associated with high prevalence of CAD risk based on the FRS (p = 0.04).
Wang et al. (2021) (42)	To test whether current and past night shift work was associated with incident atrial fibrillation and whether this association was modified by genetic vulnerability. Its associations with coronary heart disease, stroke, and heart failure were measured as a secondary aim.	Questionnaire, consultation of UK Biobank	Usual/permanent current night shifts, ≥10 years and 3-8 nights/month of lifetime night shifts were significantly associated with a higher risk of incident CHD (HR 1.22, 95% CI 1.11-1.35, HR 1.37, 95% CI 1.20-1.58 and HR 1.35, 95% CI 1.18-1.55, respectively).
Carreòn et al. (2014) (52)	To assess association between shift work and coronary artery disease	Occupational database, questionnaire	Increased CAD mortality among workers exposed 90 days or more to both shift work and carbon disulfide (SMR 1.36, 95% CI: 1.03–1.76)
Kang et al. (2016) (40)	To investigate whether shift work is related to elevated risk of coronary artery disease	Cardiac computed tomography angiography	Shift work was associated with increased risk of CAD (OR, 2.92; 95% CI 1.02 to 8.33)
Vetter et al. (2016) (45)	To determine whether rotating night shift work is associated with coronary artery disease risk	Self-administered questionnaire	Longer duration of rotating night shift work was associated with an absolute increase in CAD risk.

(continued)

Table 2. Characteristics, outcomes and main results of the checked articles. *(continued)*

Reference	Primary Outcome	Methods	Main results
Jørgensen et al. (2017) (36)	To examine the association between shift work and all-cause mortality and mortality due to CVD, cancer, diabetes, neurodegenerative and psychiatric diseases	Consultation of the Danish nurse cohort (DNC)	Association between shift work and CAD mortality among shift nurses working night shifts (HR 1.47, 95% CI 0.94–2.32)
Hermansson et al. (2018) (41)	To assess the risk for MI from an interaction between parental cardiovascular mortality or parental premature MI and shift work	Consultation of databases, questionnaire	Paternal mortality from MI or sudden cardiac death and shift work interact to increase the risk of MI in men (OR for both exposures was 2.88 (95% CI 1.75–4.57)
Wang et al. (2016) (53)	To assess ischaemic hearth disease risk/mortality	Consultation of data in the prospective Kuopio Ischemic Heart Disease Risk Factor Study cohort	Travelling work (at least 3 nights per week away from home) was strongly positively associated with acute myocardial infarction among men with ischaemic hearth disease (HR=2.45, 95% CI 1. 08 to 5.59) but not among men without (HR=0.93, 95% CI 0.43 to 2.00
Kader et al. (2022) (44)	To examine the effects of various aspects of night and shift work on the risk of incident ischemic heart disease and atrial fibrillation	Consultation of registry-based exposure data	The risk of CAD was increased among employees who the preceding year had permanent night shifts compared to those with permanent day work [hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.06–2.43] and among employees working night shifts >120 times per year compared to those who never worked night (HR 1.53, 95% CI 1.05–2.21)
Ho et al. (2022) (38)	To assess the associations between shift work and incident and fatal CVD	Consultation of UK Biobank	Increased risk of CAD (HR 1.09, 95% CI 1.03–1.15) and heart failure (HR 1.15, 95% CI 1.03–1.28) in shift-workers compared to non shift-workers
Vestergaard JM et al. (2023) (47)	To examine exposure-response relations between quantitative night work characteristics and coronary heart disease	Consultation of exposure data and health information, including information from the Danish National Patient Register	Incidence rate ratios for female and male night workers were 1.06 (95% CI: 0.97, 1.17) and 1.22 (95% CI 1.07, 1.39). Highest risks were observed in top exposure categories for several night work characteristics. No consistent exposure-response relations by number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift and consecutive night shifts were observed among the night workers of either sex

Regarding the relationship between shift work and CAD, Eng et al. [37] hypothesized that night shifts disrupt the circadian rhythm, leading to dysregulation of sleep-wake cycles, body temperature, energy metabolism, cell cycle, and hormone production. Moreover, night shift work was found to have an indirect effect through stress-related factors such as adverse psychosocial working conditions, disruption to work-life balance, insufficient time for recovery outside of work, and promotion of

unhealthy lifestyles, which could impact CAD risk. In line with these findings, Ho et al. [38], in a cohort study, demonstrated that current smoking, short sleep duration, poor sleep quality, adiposity, and higher glycated hemoglobin play a pivotal role in the mediation between shift work and CAD, representing the main potentially modifiable mediators. These findings led the authors to suggest the need for workplace interventions targeting such mediators to minimize shift workers' CVD risk.

Interestingly, in the prospective trial conducted by Havakuk et al. [39], cardiac computed tomography angiography (CCTA) showed that in shift workers, coronary artery plaques were not only more prevalent and severe than in non-SWs but, in addition, the positive coronary calcium score (CCS), a measure of the presence of CAD, was also more prevalent in SWs. These findings were obtained in individuals with no differences for risk factors and were not influenced by the clinical status of the participants; nevertheless, in this historical cohort, single-center study, most of the clinical information were collected by a telephonic questionnaire and potentially suffered from bias.

However, in line with these findings, the cross-sectional study of Kang et al. [40] demonstrated that shift work was associated with increased risk of incurring high CCS compared with day work in three different stress models focused on psychosocial, behavioral and physiological stressors that could explain the relationship between shift work and CAD: psychosocial-behavioral model [OR 2.89 (95% CI 1.07 to 7.82)]; physiological model [OR 2.92 (95% CI 1.02 to 8.33)]; psychosocial-behavioral and physiological model [OR 3.35 (95% CI 1.13 to 10.00)]. Additionally, the duration of shift work was positively associated with both the risk of atherosclerosis and the increased likelihood of developing high scores of CCS [OR 1.06 (95% CI 1.01 to 1.12)]. Studies by Havakuk et al. [39] and Kang et al. [40] revealed that shift workers face an increased risk of CAD due to the atherosclerotic process, with a higher risk of atherosclerosis associated with longer durations of shift work.

Consistent with these findings, Hermansson et al. [41], in a case-control study, reported an increased risk of short-term mortality after MI in SWs compared to non-SWs. They hypothesized that if arteries of SWs are more affected by atherosclerosis, the atherosclerotic process may have damaged the intima of blood vessels, leading to an increased risk of rupture and thrombosis when the patient is fragile due to a previous MI. These findings concur with those reported by Wang et al. [42], who proved that shift work among traveling employees was associated with acute MI in men with a previous diagnosis of CAD (HR=2.45, 95% CI 1.08 to 5.59) but not in men without CAD (HR=0.93, 95% CI 0.43 to 2.00). Moreover, the cohort study by Zhao et al. [43] revealed that SWs experiencing acute myocardial infarction face a greater risk of worsened prognosis due to reperfusion injury compared to daytime workers. This underscores the importance of maintaining normal circadian rhythm in the primary prevention of cardiovascular conditions and the clinical significance of work schedule acquisition in patients with MI for stratification and prognostic purposes.

Concerning the duration–response associations with shift work, the cohort study conducted by Kader et al. [44] demonstrated a higher risk of CAD in employees working night shifts more than 120 times per year compared to those who never worked night (HR 1.53, 95% CI 1.05–2.21). Consistent with this finding, Wang et al. [42] showed that usual/permanent current night shifts were associated with a higher risk of CAD (HR 1.22, 95% CI 1.11–1.35) and there were also associations between more than 10 years and 3–8 nights/month of night shift work exposure and the risk of CAD (HR 1.37, 95% CI 1.20–1.58 and HR 1.35, 95% CI 1.18–1.55, respectively). These findings are in line with the US Nurses' Health Study in which the risk of CAD increased with longer duration of rotating shift-work [45]; particularly, after correction for confounders, the authors observed elevated risk for 5 years or more of shift work (multivariable HR for 5-9 years, 1.12 [95% CI, 1.02-1.22]; multivariable HR for ≥10 years, 1.18 [95% CI, 1.10-1.26]; P<0.001 for trend). Previously, a meta-analysis conducted by Torquati et al. [11] proved a positive non-linear dose-response relationship that was significant after the first five years of shift work, with a 7.1% (95% CI 1.05–1.10) incremental risk of CAD events for each

subsequent 5-year exposure. Interestingly, a meta-analysis performed by Cheng et al. [46] confirmed a dose-response relationship between the prolonged duration of shift work as a continuous variable and the risk of CAD (RR 1.009; 95% CI 1.006–1.012). Furthermore, the study revealed that each 1-year extension of shift work was associated with a 0.9% enhanced risk of CAD compared to daytime workers.

On the contrary, a recent prospective cohort study conducted by Vestergaard et al. [47] found that among employees working on average 1.8 night shifts per month, only females experienced an increased risk of CAD compared to day workers (IRR 1.22 [95% CI 1.07, 1.39]) while male shift-workers didn't exhibit a higher risk compared to daytime workers (IRR 1.06 [95% CI: 0.97, 1.17]. However, no consistent exposure-response relations were observed by number of monthly night shifts, cumulative night shifts, years with rotating night shifts, years with any night shift, and consecutive night shifts among the SWs of either sex. Nevertheless, the authors emphasize that their study involved a population with low exposure to night work. Therefore, they can not conclude that there is no increased risk of CAD in employees working night shifts.

Regarding the relationship between paternal history of cardiovascular disease and CAD in shift workers, Hermansson et al. [41] found an interaction between paternal mortality from MI or sudden cardiac death and shift work on the risk of MI in men. Indeed, forty percent of MIs that occurred in the studied population were attributed to this interaction, demonstrating that paternal mortality from MI or sudden cardiac in shift workers led to a higher risk of MI than in daytime workers. Given this finding, the authors suggest investigating the medical history of paternal mortality from MI or sudden cardiac death when assessing susceptibility to CAD in SWs.

Only one study focused on interventions to minimize the CAD risk among SWs. In this pre-post intervention study, Mamen et al. [48] demonstrated that improvement in physical activity focusing on cardiorespiratory health among rotating shift workers in the industry can modify risk factors associated with CAD; in particular, SWs trained in healthy physical activity showed significant improvement of systolic and diastolic blood pressure, glycated hemoglobin (HbA1c), body mass and cholesterol ($p < 0.05$). These findings led the authors to suggest promoting physical activity as a strategic way to minimize the impact of shift work on workers' health and CAD risk. Nevertheless, Holtermann et al. [49], in the Copenhagen General Population Study, observed that higher leisure time physical activity was associated with reduced risk of major cardiac events and all-cause mortality. In contrast, higher occupational physical activity was associated with increased risks, independent of each other. These findings highlighted the independent association of physical activity with the risk of major cardiac events and all-cause mortality. They supported the physical activity paradox given the contrasting health effect of leisure time physical activity and occupational physical activity.

4.1 Limitations

This study has some limitations. The limited number of manuscripts included in this study does not make it possible to draw strong conclusions; indeed the focus of the present review was limited to CAD and didn't consider all the CVDs, therefore leading to select a small number of articles. The manuscripts included in this study suffer from differences in the criteria adopted for assessing CAD and the analysis of confounders. Two of the fifteen included studies were cross-sectional. Consequently, the nature of these studies limited the assessment of temporality and could not establish a causal relationship between shift work and CAD. The quantification of risk exposure (duration and type of shift work) as a quantitative measure of the occupational risk factor is not well quantified and only by a few studies. Finally, our systematic review did not consider the presence of quantitative measures of risk exposure in the selection of manuscripts.

5. Conclusions

Data on CAD risk among SWs are lacking in the current literature, and international guidelines do not provide subpopulation measures to prevent CAD.

Although the findings of the present systematic review point in the same direction and highlight a

relationship between shift work and the occurrence of CAD, more studies are required to clarify better the role of different variables as confounders, mediators, or effect modifiers. Moreover, as most of the selected papers did not quantify exposure to shift work, future studies are needed to fill this major gap.

Several studies have proven modifiable factors at both the individual and organizational levels to be common confounders for exposure-outcome and mediator–outcome relationships. Nevertheless, to date, the data regarding management interventions focused on the risk of CAD among SWs are lacking, and therefore, a special effort is required to detect strategic ways to minimize the likelihood of CAD occurrence in SWs.

Evidence-based guidelines are required to prevent and screen CAD in SWs. These guidelines should focus on understanding and addressing the increased risk of CAD associated with disrupted circadian rhythms and occupational factors.

Supplementary Materials: Supplementary material A: Search strategies.

Institutional Review Board Statement: Not applicable.

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References

1. Shahjehan RD, Bhutta BS. Coronary Artery Disease. 2023 Aug 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 33231974.
2. National Heart, Lung, and Blood Institute (U.S.) https://www.nhlbi.nih.gov/health/coronary-heart-disease [Last Accessed 28.02.2024].
3. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases Writing Group. (2020). Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 76(25), 2982-3021.
4. Bauersachs R, Zeymer U, Brière JB, et al. Burden of coronary artery disease and peripheral artery disease: a literature review. *Cardiovasc Ther*. 2019;2019:8295054.
5. Ralapanawa U, Sivakanesan R. Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. *J Epidemiol Glob Health*. 2021;11(2):169-177.
6. Pelletier-Galarneau M, Vandenbroucke E, Lu M, Li O. Characteristics and key differences between patient populations receiving imaging modalities for coronary artery disease diagnosis in the US. *BMC Cardiovasc Disord*. 2023;23(1):251.
7. World Health Organization; Cardiovascular Diseases (CVDs). Year: 2021. https://www.who.int/news-room /fact-sheets/detail/cardiovascular-disea ses-(cvds).
8. Ahmadi M, Lanphear B. The impact of clinical and population strategies on coronary heart disease mortality: an assessment of Rose's big idea. *BMC Public Health*. 2022;22(1):14.
9. Thomas C, Power C. Shift work and risk factors for cardiovascular disease: a study at age 45 years in the 1958 British birth cohort. *Eur J Epidemiol*. 2010;25(5):305-14. Doi: 10.1007/s10654-010-9438-4. Epub 2010 Mar 18. PMID: 20237824.
10. Shiffer D, Minonzio M, Dipaola F, et al. Effects of Clockwise and Counterclockwise Job Shift Work Rotation on Sleep and Work-Life Balance on Hospital Nurses. *Int J Environ Res Public Health*. 2018;15(9):2038.
11. Torquati L, Mielke GI, Brown WJ, Kolbe-Alexander T. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose-response relationship. *Scand J Work Environ Health*. 2018;44(3):229-238.
12. Fujino Y, Iso H, Tamakoshi A, et al. Japanese Collaborative Cohort Study Group. A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. *Am J Epidemiol*. 2006;164(2):128-35.
13. Thomas C, Power C. Shift work and risk factors for cardiovascular disease: a study at age 45 years in the 1958 British birth cohort. *Eur J Epidemiol*. 2010;25(5):305-14.
14. Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health*. 1999;25(2):85-99.
15. Farha, Rana Abu, Eman Alefishat. "Shift work and the risk of cardiovascular diseases and metabolic syndrome among Jordanian employees." Oman medical journal 33.3 (2018): 235.
16. Buijs RM, Kreier F. The metabolic syndrome: a brain disease? *J Neuroendocrinol*. 2006;18(9):715-6.

17. Furlan R, Barbic F, Piazza S, Tinelli M, Seghizzi P, Malliani A. Modifications of cardiac autonomic profile associated with a shift schedule of work. *Circulation*. 2000;102(16):1912-6.
18. Dutheil F, Baker JS, Mermillod M, et al. Shift work, and particularly permanent night shifts, promote dyslipidaemia: A systematic review and meta-analysis. *Atherosclerosis*. 2020;313:156-169.
19. Yang X, Di W, Zeng Y, et al. Association between shift work and risk of metabolic syndrome: A systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis*. 2021;31(10):2792-2799.
20. Dicom AR, Huang X, Hilal S. Association between Shift Work Schedules and Cardiovascular Events in a Multi-Ethnic Cohort. *Int J Environ Res Public Health*. 2023;20(3):2047.
21. D'Ettorre G, Pellicani V, Greco M, Caroli A, Mazzotta M. Metabolic syndrome in shift healthcare workers. *Med Lav*. 2019;110(4):285-292.
22. Civelek E, Ozturk Civelek D, Akyel YK, Kaleli Durman D, Okyar A. Circadian Dysfunction in Adipose Tissue: Chronotherapy in Metabolic Diseases. *Biology* (Basel). 2023;12(8):1077. Doi: 10.3390/biology12081077. PMID: 37626963; PMCID: PMC10452180.
23. Vyas MV, Garg AX, Iansavichus AV. Shift work and vascular events: systematic review and meta-analysis. *BMJ*. 2012;345:e4800. Doi: 10.1136/bmj.e4800
24. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med*. 2011;8(12):e1001141.
25. Rashnuodi P, Afshari D, Shirali GA, et al. Metabolic syndrome and its relationship with shift work in petrochemical workers. *Work*. 2022;71(4):1175-1182.
26. Kalsbeek A, Kreier F, Fliers E, et al. Minireview: Circadian control of metabolism by the suprachiasmatic nuclei. *Endocrinology*. 2007;148(12):5635-9.
27. Poetsch MS, Strano A, Guan K. Role of Leptin in Cardiovascular Diseases. *Front Endocrinol* (Lausanne). 2020;11:354.
28. Li W, Yu K, Jia N, et al. Past Shift Work and Incident Coronary Heart Disease in Retired Workers: A Prospective Cohort Study. *Am J Epidemiol*. 2021;190(9):1821-1829.
29. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Geneva, Switzerland: World Health Organization; 2008. https://icd.who.int/browse10/2008/en#/ I20-I25. [Last Accessed 13.12.2023].
30. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108(20):2543-9. Doi: 10.1161/01.CIR.0000100560.46946.EA
31. Härmä M, Gustavsson P, Kolstad HA. Shift work and cardiovascular disease - do the new studies add to our knowledge? *Scand J Work Environ Health*. 2018;44(3):225-228.
32. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007;7:16.
33. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. [Last Accessed on 15.022024)]; Available online:http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
34. Colaprico C, Grima D, Shaholli D, Imperiale I, La Torre G. Workplace Bullying in Italy: A Systematic Review and Meta-Analysis. *Med Lav*. 2023;114(6):e2023049.
35. Takkouche, Bahi, and Guy Norman. "PRISMA statement." Epidemiology. 22.1 (2011): 128.
36. Jørgensen JT, Karlsen S, Stayner L, Hansen J, Andersen ZJ. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health*. 2017;43(2):117-126. Doi: 10.5271/sjweh.3612
37. Eng A, Denison HJ, Corbin M, et al. Long working hours, sedentary work, noise, night shifts and risk of ischaemic heart disease. *Heart*. 2023;109(5):372-379. Doi: 10.1136/heartjnl-2022-320999
38. Ho FK, Celis-Morales C, Gray SR, Demou E, Mackay D, et al. Association and pathways between shift work and cardiovascular disease: a prospective cohort study of 238 661 participants from UK Biobank. *Int J Epidemiol*. 2022;51(2):579-590.
39. Havakuk O, Zukerman N, Flint N. Shift Work and the Risk of Coronary Artery Disease: A Cardiac Computed Tomography Angiography Study. *Cardiology*. 2018;139(1):11-16.
40. Kang W, Park WJ, Jang KH, et al. Coronary artery atherosclerosis associated with shift work in chemical plant workers by using coronary CT angiography. *Occup Environ Med*. 2016;73(8):501-5.
41. Hermansson J, Hallqvist J, Karlsson B, et al. Shift work, parental cardiovascular disease and myocardial infarction in males. *Occup Med* (Lond). 2018;68(2):120-125. Doi: 10.1093/occmed/kqy008
42. Wang N, Sun Y, Zhang H, et al. Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease. *Eur Heart J*. 2021;42(40):4180-4188. Doi: 10.1093/eurheartj/ehab505
43. Zhao Y, Lu X, Wan F, Gao L, et al. Disruption of Circadian Rhythms by Shift Work Exacerbates Reperfusion Injury in Myocardial Infarction. *J Am Coll Cardiol*. 2022;79(21):2097-2115.
44. Kader M, Selander J, Andersson T, et al. Night and shift work characteristics and incident ischemic heart disease and atrial fibrillation among healthcare employees - a

prospective cohort study. *Scand J Work Environ Health*. 2022;48(7):520-529.
45. Vetter C, Devore EE, Wegrzyn LR, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. *JAMA*. 2016;315(16):1726-34.
46. Cheng M, He H, Wang D, et al. Shift work and ischaemic heart disease: meta-analysis and dose-response relationship. *Occup Med* (Lond). 2019;69(3):182-188.
47. Vestergaard JM, Dalbøge A, Bonde JPE, et al. Night shift work characteristics and risk of incident coronary heart disease among health care workers: national cohort study. *Int J Epidemiol*. 2023:dyad126. Doi: 10.1093/ije/dyad126. Epub ahead of print
48. Mamen A, Øvstebø R, Sirnes PA, et al. High-Intensity Training Reduces CVD Risk Factors among Rotating Shift Workers: An Eight-Week Intervention in Industry. *Int J Environ Res Public Health*. 2020;17(11):3943.
49. Holtermann A, Schnohr P, Nordestgaard BG, Marott JL. The physical activity paradox in cardiovascular disease and all-cause mortality: the contemporary Copenhagen General Population Study with 104 046 adults. *Eur Heart J*. 2021;42(15):1499-1511.
50. Barger LK, Rajaratnam SMW, Cannon CP, et al. Short Sleep Duration, Obstructive Sleep Apnea, Shiftwork, and the Risk of Adverse Cardiovascular Events in Patients After an Acute Coronary Syndrome. *J Am Heart Assoc*. 2017;6(10):e006959.
51. Solymanzadeh F, Rokhafroz D, Asadizaker M, Dastoorpoor M. Prediction of risk of coronary artery disease based on the Framingham risk score in association with shift work among nurses. *Int J Occup Saf Ergon*. 2023;29(1):56-61.
52. Carreón T, Hein MJ, Hanley KW, et al. Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and o-toluidine at a chemical manufacturing plant. *Am J Ind Med*. 2014;57(4):398-411.
53. Wang A, Arah OA, Kauhanen J, Krause N. Shift work and 20-year incidence of acute myocardial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. *Occup Environ Med*. 2016;73(9):588-94.

Supplemetary Materials

Supplementary Material A

Pubmed Search Strategy:

(Ischemic Heart Disease [Mesh] OR Coronary Heart Disease [Mesh] OR Coronary Artery Disease [Mesh] OR Myocardial Infarction [Mesh]) AND (Shift Work [Mesh] OR Rotating Shift Work [Mesh] OR Night Shift Work [Mesh] OR Irregular Work Schedule [Mesh])

La Medicina del Lavoro

Reviews, Commentaries, Perspectives

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Exposure Assessment and Monitoring of Antiblastic Drugs Preparation in Health Care Settings: A Systematic Review

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Keywords: Antineoplastic Drugs; Cytotoxic Drugs; Healthcare Workers; Risk Assessment; Risk Management

Summary

Several antiblastic drugs (ADs) are classified as carcinogenic, mutagenic, and/or toxic for reproduction. Despite established guidelines and safe handling technologies, ADs contamination of the work environments could occur in healthcare settings, leading to potential exposure of healthcare staff. This systematic review investigates the main techniques and practices for assessing ADs occupational exposure in healthcare settings. The reviewed studies unveil that workplace contamination by ADs appears to be a still-topical problem in healthcare settings. These issues are linked to difficulties in guaranteeing: (i) the adherence to standardized protocols when dealing with ADs, (ii) the effective use of personal protective equipment by operators involved in the administration or management of ADs, (iii) a comprehensive training of the healthcare personnel, and (iv) a thorough health surveillance of exposed workers. A "multi-parametric" approach emerges as a desirable strategy for exposure assessment. In parallel, exposure assessment should coincide with introducing novel technologies to minimize exposure (i.e., risk management). Assessment must consider various departments and health operators susceptible to ADs contamination, with a focus extended beyond worst-case scenarios, also considering activities like surface cleaning and logistical tasks related to ADs management. A comprehensive approach in ADs risk assessment enables the evaluation of distinct substance behaviors and subsequent exposure routes, affording a more holistic understanding of potential risks.

1. Introduction

Occupational chemical risk in hospitals is a growing concern: both acute and chronic exposures to different substances and compounds used in these environments may, in fact, occur. Among these, exposure to formaldehyde, organic solvents, anesthetic gases, hazardous drugs (HDs), and antiblastic drugs (ADs) can have negative effects on the health of exposed workers [1, 2]. Based on the definitions provided by the American Society of Hospital Pharmacists in 1990 and by the National Institute for Occupational Safety and Health (NIOSH) in 2004, it can be stated that HDs are the greatest chemical

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hazard present in the healthcare field and one of the most dangerous chemical agents ever developed [3]. Among these hazardous agents, ADs (also known as cytotoxic drugs, antineoplastic drugs, anticancer drugs, or anticancer chemotherapy) are used to treat cancer [4, 5]. These drugs, depending on their mechanism of action, can be classified as carcinogenic, mutagenic, and/or reprotoxic [2, 4, 6, 7]; for this reason, the occupational exposure of healthcare personnel to these substances should be carefully evaluated, as exposure to ADs could be associated with potential health risks among healthcare workers [8].

The effects of both long and short-term exposure to ADs on healthcare workers are indeed well reported in the literature, ranging from nausea, vomiting, and diarrhea to eye and throat irritation, menstrual irregularities, skin reactions and skin rashes, hair loss, headache, and dizziness. ADs can also eventually lead to cancer, infertility, miscarriage, malformation, and genotoxicity [4, 9]. Exposure to ADs may occur mainly through skin absorption, followed by inhalation of drug aerosols and droplets, eye contact through a splash of liquids, ingestion, and sharps stick injury [5, 9].

In particular, occupational exposure to ADs (and related waste) can occur during various activities performed by healthcare personnel, such as (i) preparation, (ii) administration, (iii) transportation, (iv) storing of drugs, in addition to their waste treatment, which includes (v) transporting and disposing of waste and (vi) cleaning up spills [4, 5]. Despite the numerous guidelines in place regarding the use and handling of ADs, and the adoption of safe handling technologies (e.g., isolators and closed systems), the environment of the anticancer drug circuit can remain contaminated [2]. For example, in their study, Forges and collaborators [9] report how the entire circuit of the drugs could be contaminated: this can include (i) external surfaces of vials, (ii) storage rooms, (iii) gloves of the pharmacy technicians or nurse during handling and administration of drugs, (iv) infusion bags, (v) carts of care and even (vi) the patients' rooms.

The International Agency for Research on Cancer (IARC) has currently listed several ADs and two combination therapies as having an association with cancer in patients who are treated with them. In particular, eleven agents and two combined therapies have been classified as Group 1 (human carcinogens), twelve as Group 2A (probable human carcinogens), and eleven as Group 2B (possible human carcinogens) [10, 11]. It is also recognized how the use and administration of ADs are highly regulated issues in many countries. The Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe regulate the approval, labeling, and monitoring of the adverse effects of ADs. In addition to the legislation related to the use of ADs, it is important to evaluate the regulations related to the occupational exposure of workers who can be exposed to ADs. Several workers (e.g., oncologists, nurses, pharmacists, laboratory technicians, healthcare assistants, support staff, etc.) can be potentially exposed to these drugs during their jobs in hospitals, clinics, and pharmacies. In addition, cleaning and waste management personnel in healthcare facilities and workers in the pharmaceutical industry must also be considered to be potentially exposed [12].

For the reasons reported before, Professional Practice Organizations and Government Agencies published guidelines and other documents to protect workers who may be occupationally exposed during the (i) preparation, (ii) administration, (iii) cleaning of waste management of these drugs, (Table S1; supplementary materials). In particular, available guidelines generally respect the primary prevention measures and the hierarchy of control to mitigate workplace hazards throughout all their life cycle: referring to ADs that cannot be eliminated or substituted by another less toxic substance, exposure controls should be systematically implemented in the following hierarchical order of efficacy: (i) engineering controls; (ii) administrative controls; (iii) work practice controls; (iv) use of personal protective equipment (PPE). An issue referring to the management of occupational risk of ADs is that no Occupational Exposure Limit Values (such as RELs (NIOSH Recommended Exposure Limits), PELs (OSHA Permissible Exposure Limits), TLVs® (ACGIH - American Conference of Governmental Industrial Hygienists - Threshold Limit Values) or OELVs (European Union Occupational Exposure Limit Values) have been established for ADs in occupational and non-occupational fields [1, 2,

13]. Many manufacturers have internal occupational exposure limits, which are not generally available to regulatory agencies [12]. Therefore, only guidance values have been independently determined in different Countries such as Germany [14], the Netherlands [15], and the USA [16]. Guidelines for preventing ADs occupational exposure in Italy were published in 1999 [17].

Even though good practices have been defined and could be adopted during the use and handling of antiblastic agents, several studies reported how healthcare personnel could be exposed to antiblastic drugs: hospital staff handling ADs may indeed be exposed chronically to low doses of these drugs. Many studies have found the presence of these drugs in the urine of technicians, pharmacists, or nurses [18]. Available studies on exposure assessment are generally based on biological monitoring [18] and administering a questionnaire to workers (qualitative exposure assessment). In contrast, measuring ADs contamination (typically superficial contamination) for environmental exposure monitoring seems less common. Therefore, this study aims to investigate the main techniques and practices currently used for assessing exposure to ADs, highlighting the critical issues related to this topic. Since a comprehensive systematic review of biological monitoring data was recently published by Leso et al. [18], the present study is focused only on environmental monitoring and qualitative assessment techniques (i.e., administering questionnaires to potentially exposed workers) for occupational exposure assessment to ADs. After (i) a general overview of the studies considered in this review (Paragraph 3.1), the main results are presented subdivided by investigation methodology: (ii) questionnaire (Paragraph 3.2) and (iii) environmental monitoring (Paragraph 3.3). For both, the details of the application of the experimental method and the critical issues that emerged from the investigated articles are presented.

2. Methods

The results outcomes from three different databases (Scopus, Web of Science, and PubMed) are considered in this review. A list of keywords is arranged for each database in a search query, as reported in Table S2 (Supplementary materials): 835 papers were found (747, 26, and 62 papers in Scopus Web of Science and PubMed, respectively). Duplicates (n=66) were removed from the total number of papers. The articles have been, therefore, screened by (i) title (511 papers removed), (ii) abstract (143 papers removed), and (iii) publication year (36 papers removed). The remaining papers (full-text reading) are then selected following the inclusion and exclusion criteria chosen *a priori*. In particular, only scientific papers written in English are considered in this review, excluding conference papers and review articles. Further, articles are then selected based on consistency with the aims of this study. Thus, studies concerning occupational exposure to ADs published in 2010 that (a) performed environmental monitoring, (b) reported a risk assessment section, and (c) reported a risk management section. Only the articles that meet the above-mentioned inclusion criteria and aims of the review are examined. After that, 48 papers are finally included in this review (Table S3; Supplemental materials). Phases i-iii, as well as the screening process of article summaries, are conducted separately (and double-checked) by different authors (FB, CZ, AZ, AS), to reduce operator-related errors. The papers to be reviewed were selected following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria guidelines [19, 20]. A flowchart of the literature research and review process is reported in Figure 1.

3. Results

3.1. General Description of the Considered Studies

The supplementary materials report a general description of the reviewed articles, focusing on the period (Table S4) and geographical distribution (Table S5) of the study and of the investigated structures (Table S6).

3.1.1. Exposure and Risk Assessment Methods

The methods used in the reviewed studies for occupational exposure to ADs and risk assessment are

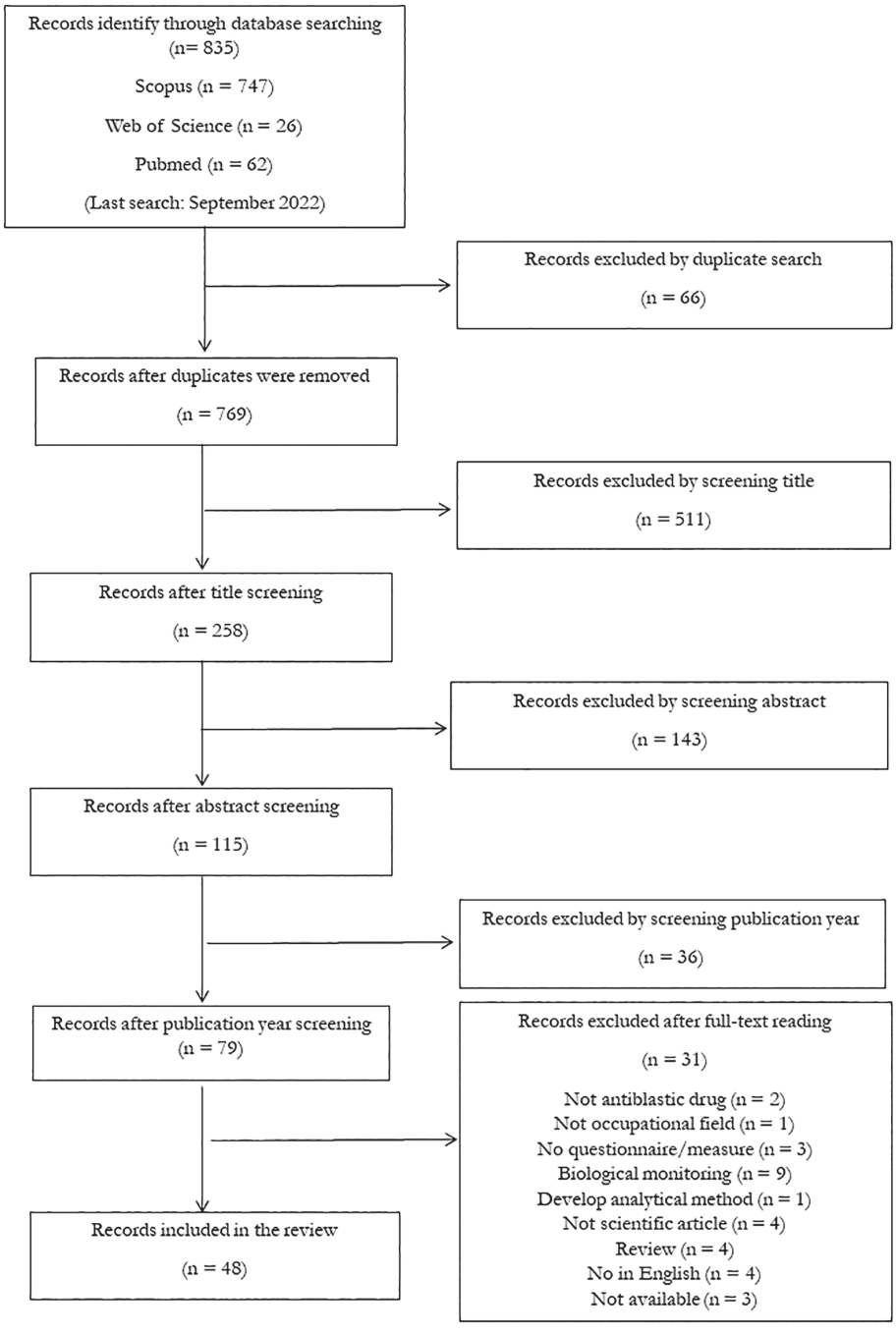

Figure 1. Flowchart of the literature research.

divided into two groups. The first group is "questionnaire and survey", which includes survey investigation methods intended to collect information about a group of workers under study and the statistical monitoring of consequences on health conditions due to exposure to ADs and other external variables that influence the cytotoxic consequences. The second group of methods is called "environmental monitoring" studies, which include sampling procedures for assessing environmental contamination, especially on working surfaces and tools. On a database of 48 selected articles (Table 1), 26 (54%)

show evidence of environmental monitoring study techniques. Of these, 23% of the studies also provide a questionnaire submitted to the workers involved (strictly restricted to healthcare workers) and the working conditions. The remaining 11 articles (23%) are only on a questionnaire submitted to involved workers, investigating risk perception among healthcare workers, knowledge of the guidelines by medical personnel, and compliance to guidelines while performing the daily job tasks (workers' self-assessment). Two of the questionnaire-based studies are dedicated to the use and knowledge of modern technologies for the management of risk posed by ADs in the medical field, which are Hyperthermic intraperitoneal chemotherapy and Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) [21, 22].

3.1.2. Investigated Population

In most (56%) of the reviewed studies (considering both environmental contamination monitoring studies and survey investigations), the healthcare workers involved in the studies are nurses (anyhow, several studies investigated more than one professional figure): in fact, the nursing staff typically manages the ADs in each step of their administration to the patient, making this category of healthcare workers a precious source of information both in relation to the medical skills that require exposure to ADs and about information of a demographic nature.

The second most abundant group of investigated workers in the reviewed studies (31%) is the one that included pharmacists and pharmacy technicians responsible for the preparation of drugs (Table 2). As regards the role of pharmacists, it is understandable that almost a third of the personnel involved in the studies investigated fall into this professional category, given that the pharmaceutical department is the one most afflicted by environmental drug contamination.

Table 1. Number (and percentage of the total - 48 studies) of reviewed articles divided according to the adopted exposure and risk assessment method.

Type of Study	N (%)	References
Measurement-based	26 (54%)	[6, 8, 9, 15, 23-44]
Questionnaire-based	11 (23%)	[3, 5, 22, 45-52]
Both measurement- and questionnaire-based	11 (23%)	[13, 21, 53-61]

3.1.3. Work Task

The results relating to the activities and procedures undertaken by the employees (Table 3) confirm those previously obtained about the professional classification of the healthcare workers (Table 2). The administration of medications, which includes dosage, intravenous injection, and patient care, comprehends more than half (54%) of the study activities described in the articles, closely followed by the preparation of drugs (40%), which includes all the pharmaceutical procedures. The same study often assessed the exposure to ADs for more than one work task or procedure. Only a few studies consider other peculiar activities, such as cleaning

Table 2. The number (and percentage of the total 48 studies) of reviewed articles was divided according to the classification of healthcare workers in study groups. n.a.: information not available and/or details not further described in the reviewed articles.

Medical Professionals and Healthcare Workers	N (%)	References
Nurses	27 (56%)	[3, 5, 8, 9, 13, 21, 29-32, 39, 42, 44-48, 50-53, 55, 56, 58-61]
Pharmacy technicians (and/or pharmacists and/or employees involved in the preparation of drugs)	15 (31%)	[3, 6, 13, 28, 29, 36, 39, 40, 43, 44, 46, 53, 58, 59, 61]
Other healthcare workers (e.g., medical staff (surgeons, doctors, anesthetists, etc.))	21 (44%)	[3, 21, 22, 25, 29, 30, 32, 33, 35, 40-42, 45, 47-50, 54, 57-59]
n.a.	7 (15%)	[15, 23, 24, 26, 34, 37, 38]

Table 3. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the classification of the assessed work tasks. n.a.: information not available and/or details not further described in the reviewed articles.

Work Tasks	N (%)	References
ADs administration	26 (54%)	[13, 21, 27-31, 33, 35, 38, 40, 41, 43-49, 51, 53-56, 58, 59]
ADs preparation	19 (40%)	[13, 23, 24, 28, 29, 31, 35-37, 39-44, 49, 53, 58, 59]
Cleaning	5 (10%)	[23, 33, 48, 59, 60]
Other activities	9 (17%)	[8, 15, 22, 23, 25-27, 59, 61]
n.a.	9 (17%)	[3, 5, 6, 9, 32, 34, 50, 52, 57]

Table 4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according the antiblastic drugs analyzed in studies under review. n.a.: information not available and/or details not further described in the reviewed articles.

Antiblastic Drugs	N (%)	References
Cyclophosphamide	24 (50%)	[6, 9, 13, 15, 23, 24, 26-30, 33, 34, 37-39, 41-44, 53, 54, 56, 57]
Ifosfamide	11 (23%)	[6, 9, 13, 15, 26, 34, 37, 39, 53, 54, 57]
5-flourouracil	17 (35%)	[6, 15, 24, 30, 35, 37, 38, 40, 42-44, 53-55, 57-59]
Methotrexate	5 (10%)	[15, 28, 40, 54, 57]
Cytarbine	3 (6%)	[25, 53, 59]
Paclitaxel	8 (17%)	[6, 9, 25, 43, 44, 53, 54, 57]
Platinum	3 (6%)	[21, 30, 54]
Gemcitabine	7 (15%)	[6, 13, 25, 38, 40, 54, 58]
Other	19 (40%)	[3, 6, 8, 9, 13, 15, 21, 22, 24, 26, 32, 35, 36, 40, 46-48, 51, 54]
n.a.	8 (17%)	[5, 31, 45, 49, 50, 52, 60, 61]

surfaces and medical tools and logistic activities (e.g., packing, storage, and transportation of drugs), taken into consideration in 10% and 17% of the studies, respectively. It is noteworthy that personnel assigned to these tasks have not been consulted or questioned. This could be due, on the one hand, to the fact that some categories of potentially exposed workers (for example, cleaning workers) were not included in the studies, but on the other hand, that cleaning and logistical activities could be delegated to medical staff (increasing their probable routes of exposure).

3.1.4. Antiblastic Drugs

Most studies provide an extended knowledge about the evaluated hazardous compounds (Table 4). Cyclophosphamide (CP; Formula: $C_7H_{15}Cl_2N_2O_2P$; CAS Number: 50-18-0), is used in most of the reviewed studies (52%) as an indicator of workplace contamination. However, most of the reviewed studies do not rely on one drug acting as an indicator of contamination but rather consider different ADs, thus allowing to cover a greater number of case studies. The set of contamination indicator substances identified in the reviewed articles is narrowed down to 8 major known drugs, described below, among the hundreds of available ADs. IARC has taken steps to group and evaluate these medicines capable of inhibiting cell division and growth; some of these substances fall into Group 1 of human carcinogens [2, 58]. The availability of various contamination indicators allows the investigation of the different behaviors of substances and, consequently, the different ways of contamination to which medical personnel may be exposed [6]. After CP, the other most common ADs considered in the reviewed studies are: (i) 5-fluorouracil (Formula: $C_4H_3FN_2O_2$; CAS Number: 51-21-8) (35% of the reviewed studies);

(ii) Ifosfamide (Formula: $C_7H_{15}Cl_2N_2O_2P$; CAS number: 377873-2) (23%); (iii) Paclitaxel (Formula: $C_{47}H_{51}NO_{14}$; CAS Number: 33069-62-4) (17%); (iv) Gemcitabine (Formula: $C_9H_{11}F_2N_3O_4$; CAS Number: 95058-81-4) (15%); (v) Methotrexate (Formula: $C_{20}H_{22}N_8O_5$; CAS Number: 59-05-2) (10%); (vi) Cytarabine (Formula: $C_9H_{13}N_3O_5$; CAS Number: 147-94-4) (6%). A small percentage of the reviewed studies (6%) use platinum as an indicator of the presence of ADs, as this element is present in the molecular structure of cisplatin (cis-diamminedichloroplatinum (II); Formula: $Pt(NH_3)_2Cl_2$; CAS Number 15663-27-1). Finally, a limited percentage of articles (17%) do not provide detailed information regarding the specific ADs considered indicators of environmental contamination. Still, it is understandable to classify these articles as descriptive of statistical surveys focused on training, occupational risk, and demographic information relating to healthcare personnel. Therefore, they are not oriented toward surface measurements and sampling (Table 4).

3.2. Questionnaire-Based Risk Assessment

As previously stated, 22 (46%) of the reviewed studies (Table 1) rely on questionnaire-based methods of investigation for what concerns both cytotoxic and non-cytotoxic variables that may influence the evaluation of occupational risk rates among healthcare workers. 9 out of these 22 articles add the survey investigation to the antiblastic drugs-detection campaign, considering, therefore, the questionnaire complementary to the study of contamination in the working environment. The entirety of the articles carries enough information to classify them into four non-mutually excludable categories: (i) interview or oral examination (5%); (ii) survey (50%); (iii) standardized questionnaire or demographic study (45%); (iv) other (such as daily diaries kept by the employees, or other forms of questionnaire, 15%) (Table 1). Often, when the questionnaire plays an additional role in the measurement study design, this investigative method is focused more on the demographic aspects of the study groups (e.g., age, sex, nature of occupation, work experience, years of service, job, etc.) rather than the elements which may affect the results on occupational risk rates and/or the employees' exposure to ADs. Each study's average number of involved subjects (described as "medical professionals") is 266, calculated based on various cases. Ranking the articles based on participation, i.e., the number of subjects involved in the reviewed studies, 5 classes of numerousness can be defined. Only 5 % of the reviewed studies involved (i) over 1000 subjects or (ii) from 500 to 1000 subjects.

Most of the reviewed studies (35%) involved between 100 and 500 interviewed healthcare workers, followed on an equal footing by survey groups formed by (iii) 50 to 100 (20%) and (iv) 10 to 50 workers (20%). For what concern the contents of the questionnaires (Table 5), 6 out of 20 articles do not provide specific information about cytotoxic variables and/or previous health conditions capable of influencing – and further increasing – the probability of contracting tumors and/or other health problems; 4 of these studies are focused on the specific training of personnel in the administration of Ads.

In their article, Asefa and collaborators [5] illustrate a questionnaire-based study on three major sectors: demographic characterization of involved subjects, knowledge and practice on safe handling of drugs, and use of personal protective equipment. Further, 2 out of 6 articles [22,45] are survey-based studies revolving around the practice of HIPEC procedures (as in, the administration of a hyperthermic solution with a high concentration of chemotherapy directly into the peritoneal cavity); questions about the training and knowledge of specialized personnel and the availability of PPE. One of these also takes into consideration the PIPAC therapy, as in a locoregional therapy for peritoneal carcinomatosis. Another study [57] mainly focuses on the compliance of healthcare personnel to the correct use of PPE. The other three studies investigate risk perception and management after implementing control programs for ADs. Of the remaining 14 articles, six do not detect, among the study groups, any relevant variables known to have cytotoxic consequences on the exposed subjects. These mentioned variables concern the exposure to first- and second-hand smoke, to radiations (specifically, those common in the healthcare environment, such as ultraviolet and X radiation), the consumption of alcohol and other drugs, and previous health conditions.

Table 5. Number (and percentage of the total- 20 studies) of reviewed articles, divided according to the characteristics of questionnaires. PPE: Personal Protective Equipment**.**

Descriptive table of questionnaires	N (%)	References
Type of questionnaire		
Interview (oral examination of subjects)	1 (5%)	[48]
Survey and/or study population	10 (50%)	[22, 45, 46, 50-54, 56, 57]
Standardized questionnaire on general information	9 (45%)	[3, 5, 45, 47, 53, 55, 56, 58, 59]
Other	3 (15%)	[48, 53, 58, 60, 61]
Information on variables known to influence cytotoxic risk		
Smoking and/or second-hand smoke exposure	5 (25%)	[53, 55, 56, 58, 59]
Alcohol and drug consumption	3 (15%)	[55, 56, 59]
Exposure to radiation and chemical	6 (30%)	[47, 51, 53, 55, 56, 58]
Previous health conditions and medical history	5 (25%)	[53, 55, 56, 59]
Information on training and/or use of PPE		
Information on training and/or use of PPE provided in the study	11 (55%)	[3, 45-48, 51-54, 56, 57, 60, 61]
Information on training and/or use of PPE not provided in the study	9 (45%)	[5, 21, 22, 39, 49, 50, 55, 58, 59]

Among the 8 studies focused on exposure to cytotoxic risks, it is consistent that the element that most contributes to the increase in the probability of cytotoxic and carcinogenic risk in the medical field is radiation, used as a diagnostic tool. It is also interesting to note how the previous health conditions of the workers have equal weight to the exposure to tobacco smoke (25% of studies confirm both the presence of smokers among the subjects and previous pathologies among those same groups); this confirms the influence of external and subjective factors in the development of pathologies – in this case, linked to exposure to Ads – and the incidence of active and passive smoking on health conditions.

Regarding the information on the training of employees and their knowledge and use of PPE, most questionnaire-based studies (55%) deemed it necessary to explore this aspect of the medical profession. One of these studies not only relies on a questionnaire but also explores in depth the handling practices and events related to the manner of use of Ads and the specific use of PPE during the preparation and administration of drugs through a 6-week diary per subject [53]. This led to a detailed study description, a defined stratification of the personnel involved, and a deep knowledge of the techniques, guidelines, and materials used.

3.2.2. Overall Comment and Critical Issues

The analysis of the information summarized in the questionnaires provides an overview of some critical issues concerning the correlation between guidelines and/or training provided to staff and widespread contamination in hospital working environments. Of the 20 articles, 9 do not give evidence of the supply and use by personnel of PPE [5, 21, 22, 39, 49, 50, 55, 58, 59], and 4 of these [21, 55, 58, 59] describe the evidence of widespread contamination in the workplace due precisely to the lack of training and the incorrect or non-existent use of PPE. Of the 4 studies that highlight a widespread problem of surface contamination, 2 of these [21, 58] delve into the question relating to the lack of guidelines and/or specific training of medical personnel: the administration of drugs in oncological departments appears to be the area where it occurs most risky contact with medicines, reaching situations of exposure by dermal contact, by hand-to-mouth contact or inhalation of vapors. A particular case [56], however, provides evidence of how, while implementing incentive programs for the use of PPE and adopting international guidelines for the management of occupational risk provided by the American Society of Health-System Pharmacists

(ASHP), the NIOSH and the US OSHA (Occupational Safety and Health Administration), there remains a detectable residual genotoxic risk; therefore, there is a definable probability of contracting tumors following exposure to this family of drugs.

The lack of a staff training and education program on the risks of managing ADs is also reflected in the recurrence of cases of occupational accidents, such as accidental drug spills and injections. It should be noted that health surveillance must be arranged for workers exposed to ADs for whom the risk assessment results reveal a risk to health (and the health surveillance program should be specific to the type of exposure defined based on the risk assessment results).

Generally speaking, health surveillance can include detecting early and reversible signs of occupational diseases and contribute to promoting a safe and healthy working environment. To this end, it may be useful to collect as much relevant information as necessary for this purpose [2]. Anyhow, specific medical surveillance for personnel involved in managing and administering antiblastic agents is completely lacking (or, rather, is not documented) in the reviewed studies. Even when included, employee health monitoring programs appear to be insufficient.

3.3. Environmental Monitoring of Exposure to ADs

As said, environmental monitoring of contamination from ADs is one of the policies recommended by the authorities, especially in the European context. European Policy Recommendations underline the importance of defining procedures for detecting workplace AD contamination to identify the vehicles and routes of exposure and improve the efficiency of prevention and protection of the medical personnel [2]. As previously stated, 37 (77%) studies considered in this systematic review are based on the sampling of surfaces to determine the environmental contamination by ADs drugs in a hospital setting (Table 5). The sampling techniques adopted in the reviewed articles pertain exclusively to environmental sampling methods; therefore, biological sampling methods will be excluded, although sometimes cited within the considered sources, even if previous publications face the issue of contamination by cytotoxic drugs, focusing their method on the biological tracking and monitoring of drugs through the occupational process of preparation and administration of said drugs. The undeniable impact on subjects exposed to ADs is highlighted in numerous previous studies. Indeed, several studies demonstrate that remarkable portions of healthcare workers may have traces of these substances or their metabolites in biological fluids [18]. The biological monitoring helped to show the correlation between the detected presence of drugs in bodily fluids of medical workers (such as urine and blood) and relevant consequences on health conditions, commonly related to skin rashes, chromosomal aberrations, and, in female subjects, to infertility and miscarriage [9].

3.3.1. Sampling Techniques

Overall, analyzing the methods for the study of spread contamination, the reviewed studies can be sorted into three main categories: (i) those based on surface wipe sampling techniques, (ii) those that rely on dermal and pad samples, and (iii) those based on air sampling methods (comprehensive of personal samples) (Table 6). Around 64% of the 37 articles report using wipe sampling techniques to detect workplace contamination. For most of these studies, information on the numerical quantity of the samplings is provided. The process is useful and inexpensive; the required materials and samples-analysis-technologies are easily accessible and imply the possibility of numerous specimens to track the contamination pattern. It is a direct consequence that the greatest amount of information regarding materials and analysis techniques was available for studies based on environmental sampling of surfaces. The reviewed articles have provided detailed data regarding the number of samplings conducted through surface sampling: most wipe-samples-based studies (around 37%) collected between 100 and 500 samples, 17% of the studies collected between 10 to 50 samples, 10% collected between 50 and 10, and between 1 and 10 samples. Few studies have sampled between 500 and 1000 surfaces (3%) and more than 1000 surfaces (3%).

Table 6. Number (and percentage of the total - 37 studies) of reviewed articles, divided according to the characteristics of measurement techniques. n.a.: information not available and/or details not further described in the reviewed articles.

Descriptive table of measurements and sampling	N (%)	References
Type of samples		
Surface Wipe Sample	24 (65%)	[13, 15, 24, 26, 28, 29, 33-35, 37, 38, 40-44, 53-59, 61]
Air and/or Personal Sample	1 (3%)	[53]
Dermal and/or Pads Samples	6 (16%)	[28, 36, 56-59]
Other	2 (5%)	[25, 31]
Support used for Surface Wipe Samples (in 24 studies in which Surface Wipe Sampling was perfomed)		
Kleenex	1 (4%)	[13]
Gauze	2 (8%)	[44, 55]
Nonwoven	9 (38%)	[24, 26, 28, 37, 38, 42, 43, 53, 59]
Other	1 (4%)	[31]
n.a.	12 (50%)	[15, 29, 33-35, 40, 41, 54, 56-58, 61]
Sampling areas (in 37 studies in which environmental sampling was performed)		
Biological Safety Cabinets	9 (24%)	[13, 29, 35, 37, 41, 42, 44, 53, 57]
Surfaces in working areas and floors	18 (49%)	[13, 15, 24, 29, 34, 35, 38, 40, 41, 43, 44, 53-57, 59, 61]
Medical tools and/or clothes/fabrics	12 (32%)	[24, 26, 28, 31, 32, 36, 38, 55-59]
Everyday activities-related surfaces and commonly used objects	7 (19%)	[32, 34, 41-44, 55]
n.a.	4 (11%)	[8, 25, 33, 60]
Analytical procedures (in 37 studies in which environmental sampling was performed)		
HPLC-MS/MS	11 (30%)	[6, 9, 13, 23, 28, 29, 34 39, 40, 53, 54]
HPLC-MS	2 (5%)	[24, 26]
HPLC-UV-Vis	3 (8%)	[37, 58, 59]
HPLC-DAD	4 (11%)	[25, 43, 44, 55]
UPLC-MS/MS	1 (3%)	[35]
GC-MS	4 (11%)	[15, 41, 42, 54]
GC-MS/MS	4 (11%)	[30, 37, 38 56]
Voltammetry	2 (5%)	[30, 54]
Other *(semi-quantitative method for tracing (UV) and for exposure assessment (modeling))*	3 (8%)	[27, 31, 36]
n.a.	4 (11%)	[8, 57, 60, 61]

Only 1 out of the considered publications [53] describe a study based on air and personal sample techniques. The study was focused on evaluating the antiblastic drug exposure of healthcare workers at 3 university-based US cancer centers, which proved to be one of the most complete and thorough studies among those considered in this review.

A more relevant percentage (16%) of the 37 articles evaluated dermal exposure and/or pad samples. This method implies the evaluation of contamination directly on subjects whose skin has been potentially exposed to ADs. Only half of them provide precise information about the collected quantity of samples. [53]

3.3.2. Methods and Techniques of Surface Wipe Sampling of ADs

Delving into the surface wipe sampling materials and techniques (Table 6), 38% of the surface-sampling-based studies rely on nonwoven fabric. Diverse types of papers and pads are quoted in the articles, showing how similar materials may be used under different circumstances and how the macro-category of non-fabric-based samples may be divided into different methods and materials of analysis. Among these studies, it is interesting to highlight examples of nonwoven tissues, such as Whatman paper wetted with sterilized water – made by acid-hardened cellulose filters – exploited in two French studies (suggesting it may be a technique mostly popular in Europe), Kimtech and Kimwipe tissue – laboratory paper towels, the first wetted with ethyl-acetate ($C_4H_8O_2$) – useful for their high absorbency and chemical passivity to perform delicate tasks of sampling, and glass fiber filter papers, wetted with water, known to be used in one of the considered studies. Two of the 30 (8%) studies conducted in Portugal present a method based on using gauze to sample surfaces. However, tissue fiber (gauze) quickly dries the biological substance. Therefore, it is necessary to ensure the material is sufficiently moistened with ethyl-acetate.

3.3.3. Sampling Areas

Knowing most articles propose a surface sampling technique, the collection of information related on sampling positions is, in the present review, specifically focused on working surfaces and medical tools (Table 6). Indeed, surfaces in working areas, such as worktops, tables, trails, preparation, and drug administration surfaces, are included in 49% of the studies. In comparison, medical tools and/or clothes and fabrics available for medical personnel closely follow with a percentage of 32%. These sampling areas are distributed within the hospital environments involved in the preparation and administration of chemotherapy drugs and the patient care units, where the drugs are administered to patients via injection or other specific chemotherapy administration techniques. As reported by Hon and collaborators [29], the stages for the sampling activities can be divided into areas to recognize the most common areas of evaluation of contamination rates: (i) the delivery of ADs through the logistic department, (ii) the drug preparation in the specific isolated room in the pharmacy department equipped with biological safety cabinets (BSCs), (iii) the transportation within the wards and through different hospital environments, (iv) the administration of drug within the patient care units and (v) the waste disposal (which represent a further biological risk of contamination and a route for occupational exposure). Particularly, since BSCs are a recurring risk management measure, it is worth noting that 24% of the studies report having practiced samplings of BSC surfaces. BSCs prove to be a useful tool to remedy the widespread contamination; in the results subsequently discussed, it will be seen how a high environmental contamination is present only in 2 of the studies in which samplings were conducted on the surfaces of the BSCs. Some "Everyday objects" (such as phones, computer devices, handles and handlebars, and other objects shared by the medical personnel) involved in the medical facilities follow as a recurrent group (19% of the studies) of items considered among the detected surfaces. It is interesting to observe how these generic tools – in the narrow sense unrelated to the healthcare activities of administering antiblastic drugs – are included in the studies almost with the same frequency as BSCs, a specific medical device thought to prevent biohazard.

3.3.4. Analytical Procedures for Analysis of ADs Samples

The analysis of the ADs samples (collected with the previously described methods) can be conducted with different analytical procedures (Table 6). Mass spectrometry (single or tandem) is the most widely used analytical technique (38% of studies are known to use this technology). Of the considered studies, 9 out of the 14 use mass spectrometry reports to couple this technique with liquid chromatography. Further, 7 of the 14 considered studies couple mass spectrometry with gas chromatography. Alternatively, methods based on ultraviolet radiation or

X-rays are relatively frequent. One article also provided specific indications regarding the software used to support analytical techniques specifically created for biomedical research (MedCalc) [31]. Focusing on wipe test sampling analytical techniques (mostly used sampling technique) used in studies of this type, this work does not provide further information regarding these techniques, as they are reported in a recent review of the literature focused precisely on this topic [62].

3.3.5. Overall Comment and Critical Issues

Contamination of the workplace by ADs could be related to incorrect practices and/or a lack of risk management measurements in the investigated workplaces [23, 37, 52, 59]. Nevertheless, it should be noted that environmental contamination is also significantly reduced in the presence of correct training and protection of personnel. Only a few studies report relevant workplace contamination by ADs [6, 23, 25, 33, 40, 41]. Further, some of the reviewed studies, characterized by a critical issue of a general nature about the hospital structure and the healthcare workers involved, focus the attention on the economic impact of risk prevention devices, on the need to make drug monitoring and tracing programs more efficient, on the guidelines to be implemented to reduce exposure and recurrence of accidental events [13, 23, 31, 42, 43, 45, 48, 51, 52, 58, 59]. It is worth noting that for more than half of the reviewed articles, it was not possible to obtain information regarding the availability and/or of correct use personal protective equipment by health professionals [3, 6, 8, 15, 22-26, 29, 32-34, 38, 40-44, 49-53, 55, 57, 58, 61]. Only 11 studies reported the availability of training programs or guidelines and procedures for drugs management and use of protective devices [6, 13, 21, 23, 28, 31, 37, 39,42, 47, 48, 51, 52, 56, 57, 59, 60].

Further, only a few of these studies report and describe the presence of a specific medical surveillance protocol [13, 21, 23, 45-47]. A relevant link could be speculated between the adoption of clear and carefully imparted procedures and guidelines to personnel, the pertinent use of PPE (more useful and efficient in protecting the healthcare worker than in preventing the spread of ADs in the workplace), and the significant decrease in the concentration of contaminating substances in the environment. Concerning the problem of accidental contamination events, it can be stated that a small proportion (approximately 17%) of studies dealing with environmental monitoring report the occurrence of occupational accidents related to drug administration [3, 13, 23, 30, 34, 41, 42, 44-49, 52, 53, 60]. In most cases, these are spills that occurred during the preparation of the equipment for administering the drug to the patient: connection between tubes, syringes, and infusion lines, or contact with previously opened vials and/or vials damaged during transport of the material between hospital wards. It is logically difficult to predict the probability of the occurrence of accidental events of this type. Still, it is possible that the recurrence of these events could be limited by defining effective and efficient work procedures and operator training. Certainly, the degree of risk to which the healthcare worker is exposed increases significantly in the absence of personal protective equipment, especially when the professional accident involves dermal contact or accidental injection following the handling of syringes and infusion systems. Two studies [31, 38] can be particularly significant regarding workplace contamination's impact on healthcare workers' health conditions and the importance of making expensive technologies for prevention and protection from exposure to cytotoxic drugs available to hospital facilities and cancer treatment centers. The first of these two studies [31] effectively highlights how a closed-system drug transfer device can contribute to a significant containment of the diffusion of surface contamination. The second study [38] illustrates the advantage of using a cytotoxic safe infusion system (CSIS, i.e., a disposable sterile infusion system, functioning through a single closed line system by the effect of gravity or exerted pressure) for drug preparation and administration. Its usefulness lies in the ability to eliminate the risk of aerosolization of ADs and to prevent the spreading of substances on surfaces following accidental events in the event of a leak. However, a limit to the dissemination of the application of this technology is its rather expensive

cost and the need of a specific training program for the use of this technology.

4. Discussion

This study investigates the main techniques and practices currently used to assess exposure to ADs. This review focuses, in particular, on the (i) administration of questionnaires to workers and (ii) the environmental sampling techniques for the assessment of workplace contamination (especially on work surfaces) by ADs. As mentioned, this study did not evaluate biological monitoring, as it was considered in a recent systematic literature review [18]. From the studies considered in this work, however, it can be highlighted that only 19% of studies (Table 1) based their exposure assessments on both environmental sampling and the administration of questionnaires. These results indicate that a "multiparametric" approach still seems not to be considered in the majority of cases: for this reason, as mentioned, the authors recommend applying both types of evaluation to conduct an overall evaluation of exposure to ADs as complete as possible.

The following discussion can be drawn from the evaluation of the results reported in the 48 articles included in this review. In general, 23% of the considered studies were based solely on administering questionnaires to workers, while 58% focused only on environmental sampling. According to the authors, using a questionnaire associated with environmental sampling (and, in the best case, biological monitoring) could be the best solution for ADs exposure evaluation and risk management. Therefore, its integrated use is recommended. Evaluation studies of this type should also be performed in association with the introduction of new technologies aimed at minimizing the worker's exposure to ADs (e.g., robotic systems, isolators, HIPEC) to evaluate their effectiveness and to evaluate the application of peculiar procedures/protocols by health professionals. Furthermore, the assessments should be carried out in the various departments affected by a possible ADs contamination and on all the operators involved in their handling and management, and not exclusively in the case that can be considered as the worst-case scenario (e.g., ADs preparation area), to coherently evaluate all the possible exposure situations to ADs. For the same reason, activities conducted by healthcare professionals, such as cleaning surfaces and medical instruments and logistic activities (e.g., packaging, storage, and ADs transport), should be better evaluated (and thus included in the monitoring protocols) in terms of their potential contribution to occupational exposure to ADs. In addition, it can be suggested to evaluate a wide range of ADs in different workplace environments, as (i) hospital facilities tend to manage a wide variety of AD depending on the chemotherapy treatments envisaged and on the technologies available, and (ii) the availability of different contamination indicators allows to investigate the different behavior of the substances and, consequently, the different route of contamination to which medical personnel can be exposed.

More specifically, administering questionnaires (also understood as interviews, oral examinations, surveys, standardized questionnaires, or demographic studies) commonly aim to investigate the worker's knowledge concerning safe managing ADs and using PPE. Specifically, some studies have focused on evaluating the correct application of the procedures indicated for peculiar tools and technologies (e.g., HIPEC). In addition to this information (and to that of a descriptive/demographic type and, although less frequent, on variables known to influence the cytotoxic risk on health), the tendency seems to be to investigate topics such as the operator's perception of the risk and its management. The results of some studies analyzed in this review show how an AD contamination situation can often be correlated with the lack of standardized procedures, the incorrect use of PPE, and an incompletely satisfactory training of healthcare workers. The lack of a staff training and education program on AD management risks is also reflected in the recurrence of workplace accidents (e.g., accidental drug injections and spills). Further, another critical issue that emerged from the evaluation of the studies based on the administration of questionnaires is related to the lack of specific medical surveillance for the personnel involved in the management and administration of antiblastic agents, which in some cases would

appear to be completely lacking. ADs environmental monitoring is one of the policies for ADs risk assessment and management recommended by most of the authorities, especially in the European context. Specifically, European Policy Recommendations underline the importance of defining procedures for the detection of drugs, identifying the routes of contamination, and improving the efficiency of prevention and protection of medical personnel. In general, it can be stated that most of the studies considered in this review focused on (i) sampling based on surface wipe sampling techniques, followed by studies (ii) based on dermal and pad samples and, albeit less numerous, (iii) on air sampling methods (comprehensive of personal sampling campaigns). Studies based on AD environmental monitoring also suggest a correlation between incorrect practices and/or lack of risk management measurements (such as the correct use of PPE) in the investigated workplaces and the widespread contamination of surfaces by ADs. On the contrary, as expected, there is a significant link between the adoption of clear and carefully imparted procedures and guidelines to personnel, the pertinent use of PPE, and the significant decrease in the contaminating substances in the environment. However, in this case, there is still a significant lack of medical surveillance programs for health workers. Nevertheless, it is noted that environmental contamination is significantly reduced in the presence of correct training and personnel protection. Finally, considering the problem related to accidental events, it can be stated that a small proportion of studies report the occurrence of occupational accidents related to drug administration, mainly attributable to the preparation of the equipment for administering the drug to the patient (e.g., the connection between tubes, syringes, and infusion lines, or contact with previously opened vials and/or vials damaged during transport of the material between hospital wards): it is difficult to make predictions regarding the occurrence of these accidental events, but it is important to underline how the recurrence of these events could be limited by defining effective and efficient work procedures.

5. Conclusions

The present review and the studies analyzed in its drafting highlight several critical issues that require particular attention.

Specifically, (i) the correct use of standardized protocols for the management and manipulation of ADs, as well as (ii) the proper use of PPE, (iii) the correct training of all personnel involved in the handling and management of these drugs and (iv) complete health surveillance are essential features for the purpose the assessment and management of occupational risk posed by ADs. Although the critical issues reported above were already well known and recognized, from the analyzed articles, the need to implement these measures still emerges today, as environmental contamination by ADs seems to be a topical problem in hospital-type environments since several healthcare professionals are still exposed to ADs, despite the adoption of protective and preventive measures [18]. In particular, the literature is not yet fully comprehensive regarding assessing exposure to Ads for certain categories of healthcare workers (e.g., workers engaged in the logistics of ADs and individuals involved in cleaning surfaces potentially contaminated by Ads). A potentially critical scenario could arise for workers tasked with cleaning surfaces of pharmaceutical isolators or robotic instruments (or, more generally, work surfaces). While these preventive systems are designed to protect the individual responsible for preparing the ADs, they may not provide optimal protection for the healthcare worker responsible for cleaning them.

Although exposure to ADs is normally kept under control, thanks to the adoption of preventive interventions, the development/improvement of personal protective equipment, and the correct training and information activities for operators, from the studies analyzed in this review still emerge some criticisms that cannot be ignored: a "new" approach, which could be defined as "multiparametric" (which includes analyses of diverse types - from questionnaires to environmental and biological sampling), is therefore necessary. This approach should allow the implementation of optimal strategies that can protect workers while maintaining the clinical efficiency of antiblastic therapy [18].

This "multi-parametric" approach can be very useful since (i) different methodologies (i.e., environmental sampling, biological monitoring, questionnaires, and interviews) obviously and necessarily provide different information, which cannot be directly compared with each other, but which can provide complementary information, thus providing a total understanding of the exposure to ADs; (ii) a certain investigation methodology can be applied when another is not usable (for example, because analytical and procedural limits).

Supplementary Materials: The following are available online, Table S1. List of documents referred to ADs; Table S2. Search query arranged for each database; Table S3. Complete list of papers found suitable and reviewed in this study; Table S4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study period (five-year intervals); Table S5. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study location (major geographical areas). Table S6. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to: a) Healthcare facilities considered in the studies under review. b) Departments and wards considered in the studies under review.

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References

1. Jana S, Chakraborty D. Chemical Risk in Hospitals: An Overview of Monitoring Strategies and International Regulatory Practical Concerns. *International Journal of Innovative Research in Engineering*. 2023;562–70.
2. European Commission. Guidance for the safe management of hazardous medicinal products at work. Second Edition. Luxembourg: Publications Office of the European Union, 2023.
3. Bernabeu-Martínez MÁ, Sánchez-Tormo J, García-Salom P, Sanz-Valero J, Wanden-Berghe C. Perception of risk of exposure in the management of hazardous drugs in home hospitalization and hospital units. *PLoS One*. 2021;16:e0253909.
4. Mahboob M, Rahman MF, Rekhadevi P V, et al. Monitoring of oxidative stress in nurses occupationally exposed to antineoplastic drugs. *Toxicol Int*. 2012; 19:20–4.
5. Asefa S, Aga F, Dinegde NG, Demie TG. Knowledge and Practices on the Safe Handling of Cytotoxic Drugs Among Oncology Nurses Working at Tertiary Teaching Hospitals in Addis Ababa, Ethiopia. *Drug Healthc Patient Saf*. 2021;13:71–80.
6. Korczowska E, Crul M, Tuerk J, Meier K. Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries—results of the MASHA project. *Eur J Oncol Pharm*. 2020;3.
7. European Parliament and Counci. Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. 2022.
8. Kumari S, Lobo DJ, Sequira L. Potential Health Risks among Oncology Staff Nurses of Selected Hospitals due to Antineoplastic Drug Exposure. *Indian J Public Health Res Dev*. 2017;8:358–61.
9. Forges F, Blanc E, Raymond B, et al. Evaluation of a safe infusion device on reducing occupational exposure of nurses to antineoplastic drugs: a comparative prospective study. Contamoins-1. *Int Arch Occup Environ Health*. 2021;94:1317–25.
10. NIOSH. N ational Institute Occupational Safety and Health (2017). Hazardous drug exposures in healthcare. Available online at: https://www.cdc.gov/niosh/topics/hazdrug/antineoplastic.html [Last Accessed 29-03-2024].
11. IARC. International Agency for Research on Cancer (2024). Agents classified by the IARC monographs. Available online at: https://monographs.iarc.who.int/agents-classified-by-the-iarc/ [Last Accessed 29-03-2024].
12. OSHA. Occupational Safety and Health Administration (2024). Controlling Occupational Exposure to Hazardous Drugs. Available online at: https://www.osha.gov/hazardous-drugs/controlling-occex [Last Accessed 29-03-2024].
13. Sottani C, Porro B, Imbriani M, Minoia C. Occupational exposure to antineoplastic drugs in four Italian health care settings. *Toxicol Lett*. 2012;213:107–15.
14. Schierl R, Böhlandt A, Nowak D. Guidance values for surface monitoring of antineoplastic drugs in German pharmacies. *Ann Occup Hyg*. 2009;53:703–11.

15. Crul M, Simons-Sanders K. Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies. *J Oncol Pharm Pract*. 2018;24:483–9.
16. Gabay M. Handling Hazardous Drugs. *Hosp Pharm*. 2014;49:811–2.
17. Ministero della Sanità. Linee-Guida per la sicurezza e la salute dei lavoratori esposti a chemioterapici antiblastici in ambiente sanitario (Repertorio Atti No. 736). Official Gazette of the Italian Republic, 07 October 1999, No 236. Rome; 1999.
18. Leso V, Sottani C, Santocono C, Russo F, Grignani E, Iavicoli I. Exposure to Antineoplastic Drugs in Occupational Settings: A Systematic Review of Biological Monitoring Data. *Int J Environ Res Public Health*. 2022;19.
19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 200; 6(7):e1000097.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
21. Ndaw S, Hanser O, Kenepekian V, , et al. Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. *Toxicol Lett*. 2018;298:171–6.
22. Ferron G, Simon L, Guyon F, et al. Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey. *Eur J Surg Oncol*. 2015;41:1361–7.
23. Acramel A, Fouque J, Blondeel-Gomes S, et al. Application of an Environmental Monitoring to Assess the Practices and Control the Risk of Occupational Exposure to Cyclophosphamide in Two Sites of a French Comprehensive Cancer Center. *Ann Work Expo Health*. 2022;66:1215–23.
24. Bobin-Dubigeon C, Amiand M, Percheron C, et al. A new, validated wipe-sampling procedure coupled to LC-MS analysis for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination. *J Anal Toxicol*. 2013;37:433–9.
25. Claraz P, Riff I, Vert C, et al. Assessment of efficacy of postinfusion tubing flushing in reducing risk of cytotoxic contamination. *Am J Health Syst Pharm*. 2020; 77:1866–73.
26. Cotteret C, Secretan P-H, Gilles-Afchain L, et al. External contamination of antineoplastic drug vials: an occupational risk to consider. *Eur J Hosp Pharm*. 2022; 29:284–6.
27. Fransman W, Kager H, Meijster T, et al. Leukemia from dermal exposure to cyclophosphamide among nurses in The Netherlands: quantitative assessment of the risk. *Ann Occup Hyg*. 2014;58:271–82.
28. Hon C-Y, Astrakianakis G, Danyluk Q, Chu W. Pilot Evaluation of Dermal Contamination by Antineoplastic Drugs among Hospital Pharmacy Personnel. *Can J Hosp Pharm*. 2011;64:327–32.
29. Hon C-Y, Teschke K, Chua P, Venners S, Nakashima L. Occupational Exposure to Antineoplastic Drugs: Identification of Job Categories Potentially Exposed throughout the Hospital Medication System. *Saf Health Work*. 2011;2:273–81.
30. Koller M, Böhlandt A, Haberl C, Nowak D, Schierl R. Environmental and biological monitoring on an oncology ward during a complete working week. *Toxicol Lett*. 2018;298:158–63.
31. Lalande L, Galy G, Dussossoy E, Noyel J-E, Pivot C. Evaluation of Safe Infusion Devices for Antineoplastic Administration. *J Infus Nurs*. 2015;38 Suppl 6:S29-35.
32. Larroque M, Arnaudguilhem C, Bouyssiere B, et al. Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy. *Toxicol Appl Pharmacol*. 2021;429:115694.
33. Azari M, Panahi D, Akbari ME, et al. Environmental Monitoring of Occupational Exposure to Cyclophosphamide Drug in Two Iranian Hospitals. *Iran J Cancer Prev*. 2017;10:e7229.
34. Mucci N, Dugheri S, Farioli A, et al. Occupational exposure to antineoplastic drugs in hospital environments: potential risk associated with contact with cyclophosphamide- and ifosfamide-contaminated surfaces. *Med Pr.* 2020;71:519–29.
35. Rossignol E, Amiand MB, Sorrieul J, Bard JM, Bobin-Dubigeon C. A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics. *J Pharmacol Toxicol Methods*. 2020; 101:106652.
36. Sadeghipour F, Lorenzini KI, Ziewitz C, Dobrinas M, Fleury M, Bonnabry P. Chemical contamination during the preparation of cytotoxics: validation protocol for operators in hospital pharmacies. *J Oncol Pharm Pract*. 2013;19:57–64.
37. Sessink PJM, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract.* 2011;17:39–48.
38. Siderov J, Kirsa S, McLauchlan R. Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device. *J Oncol Pharm Pract*. 2010;16:19–25.
39. Sottani C, Porro B, Comelli M, Imbriani M, Minoia C. An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878:2593–605.
40. Dugheri S, Bonari A, Pompilio I, Boccalon P, Mucci N, Arcangeli G. A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments. *Arh Hig Rada Toksikol*. 2018;69:226–37.

41. Sugiura S, Nakanishi H, Asano M, et al. Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan. *J Oncol Pharm Pract*. 2011;17:20–8.
42. Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T. Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide. *J Oncol Pharm Pract*. 2011;17: 14–9.
43. Viegas S, Oliveira de AC, Carolino E, Pádua M. Occupational exposure to cytotoxic drugs: the importance of surface cleaning to prevent or minimise exposure. *Arh Hig Rada Toksikol*. 2018;69:238–49.
44. Viegas S, Pádua M, Veiga AC, Carolino E, Gomes M. Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals. *Environ Monit Assess*. 2014;186:7807–18.
45. Benoist H, Eveno C, Wilson S, et al. Perception, knowledge and protective practices for surgical staff handling antineoplastic drugs during HIPEC and PIPAC. *Pleura Peritoneum*. 2022;7:77–86.
46. Boiano JM, Steege AL, Sweeney MH. Adherence to Precautionary Guidelines for Compounding Antineoplastic Drugs: A Survey of Nurses and Pharmacy Practitioners. *J Occup Environ Hyg*. 2015;12:588–602.
47. Boiano JM, Steege AL, Sweeney MH. Adherence to safe handling guidelines by health care workers who administer antineoplastic drugs. *J Occup Environ Hyg*. 2014;11:728–40.
48. Kieffer C, Verhaeghe P, Lagrassa S, et al. Preventing the contamination of hospital personnel by cytotoxic agents: evaluation and training of the para-professional healthcare workers in oncology units. *Eur J Cancer Care (Engl)*. 2015;24:404–10.
49. Constantinidis TC, Vagka E, Dallidou P, et al. Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals. *Eur J Cancer Care* (Engl). 2011;20:123–31.
50. Altini M, Bernabini M, Marchetti P, Orlando L, Rebesco B, Sirna V. Risk management of onco-hematological drugs: how and how fast can we improve? *Tumori*. 2016;102:15–29.
51. Kim O, Lee H, Jung H, Jang HJ, Pang Y, Cheong H. Korean nurses' adherence to safety guidelines for chemotherapy administration. *Eur J Oncol Nurs*. 2019;40:98–103.
52. Liu N, Lu H, Yi X-Q, Yang Y, Huang X-H. Nurses' knowledge, perceptions, and behaviors regarding antineoplastic drugs: the mediating role of protective knowledge. *Frontiers of Nursing*. 3922;9:155–63.
53. Connor TH, DeBord DG, Pretty JR, Oliver MS, Roth TS, Lees PSJ, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med.* 2010;52:1019–27.
54. Kopp B, Schierl R, Nowak D. Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings. *Int Arch Occup Environ Health*. 2013;86:47–55.
55. Ladeira C, Viegas S, Pádua M, et al. Assessment of genotoxic effects in nurses handling cytostatic drugs. *J Toxicol Environ Health A*. 2014;77:879–87.
56. Moretti M, Grollino MG, Pavanello S, et al. Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach. *Int Arch Occup Environ Health.* 2015;88:683–95.
57. Crickman R, Finnell DS. Chemotherapy Safe Handling: Limiting nursing exposure with a hazardous drug control program. *Clin J Oncol Nurs*. 2017;21:73–78.
58. Ursini CL, Omodeo Salè E, Fresegna AM, et al. Antineoplastic drug occupational exposure: a new integrated approach to evaluate exposure and early genotoxic and cytotoxic effects by no-invasive Buccal Micronucleus Cytome Assay biomarker. *Toxicol Lett*. 2019;316:20–6.
59. Villarini M, Dominici L, Piccinini R, et al. Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs. *Mutagenesis*. 2011;26:359–69.
60. Leduc-Souville B, Bertrand E, Schlatter J. Risk management of excreta in a cancer unit. *Clin J Oncol Nurs*. 2013;17:248–52.
61. Fernandes NM, Pelissari IG, Cogo LA, Santos Filha VAV Dos. Workplace Activity in Health Professionals Exposed to Chemotherapy Drugs: An Otoneurological Perspective. *Int Arch Otorhinolaryngol*. 2016;20:331–8.
62. Vermette ML, Hicks MR, Khoroush K, Teo MY, Gates BD. Wipe sampling of antineoplastic drugs from workplace surfaces: A review of analytical methods and recommendations. *Hygiene and Environmental Health Advances*. 2024;9:100089.

SUPPLEMENTARY MATERIAL

Table S1. List of documents referred to ADs. ADs: antineoplastic drugs; HDs: hazardous drugs. Document type: A: Alert; BC: Chapter of a book; D: Directive; G: Guide; GL: Guideline; LD: List of Drugs; TM: Technical Manual.

Reference	Title	Document type	Note
[1]	Guidelines for Cytotoxic (Antineoplastic) Drugs	GL	The first published guidelines for the management of ADs.
[2]	Controlling Occupational Exposure to Hazardous Drugs	TM	Withdrawn and replaced by the webpage Controlling Occupational Exposure to Hazardous Drugs.
[3]	Preventing occupational exposure to antineoplastic and other drugs in healthcare settings	A	Additional guidelines that address HDs or the equipment in which they are manipulated are reported by the NIOSH Alert.
[4]	ASHP Guidelines on Handling Hazardous Drugs	GL	Based on the NIOSH Alert.
[5]	List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings	LD	The list supersedes the 2004 list in the next NIOSH Alert and the 2014 list of HDs. The current update (2016) adds 34 drugs, five of which have safe-handling recommendations from the manufacturers.
[6]	Hazardous Drugs - Handling in Healthcare Settings	BC	Describes practice and quality standards for the handling of HDs.
[7]	Guidance for the safe management of hazardous medicinal products at work	G	This guide aims to provide an overview of the good practices available and give practical ways to reduce workers' exposure to hazardous medicinal products
[8]	Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work	D	Directive 2022/431/EU amends Directive 2004/37/EC [9] on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.

Table S2. Search query arranged for each database (last search: September 2022).

Database	Search query
Scopus	ALL ("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*") AND ALL ("occupational exposure") AND ALL ("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk") AND ALL ("healthcare*" OR "healthcare worker*" OR "care worker*")
Web of Science	(((ALL=("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*")) AND ALL=("occupational exposure")) AND ALL=("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk")) AND ALL=("healthcare*" OR "healthcare worker*" OR "care worker*")
PubMed	((("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*") AND ("occupational exposure")) AND ("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk")) AND ("healthcare*" OR "healthcare worker*" OR "care worker*")

Table SM3. Complete list of papers found suitable and reviewed in this study.

Reference	First Author	Publication year	Title	Source	DOI
[10]	Acramel et al.	2022	Application of an Environmental Monitoring to Assess the Practices and Control the Risk of Occupational Exposure to Cyclophosphamide in Two Sites of a French Comprehensive Cancer Center	Ann Work Expo Health. 2022; 66(9):1215-1223	10.1093/annweh/wn.a.ac035
[11]	Altini et al.	2016	Risk management of onco-hematological drugs: How and how fast can we improve?	Tumori. 2016; 102(Suppl 1):15-29.	10.5301/tj.5000540
[12]	Asefa et al.	2021	Knowledge and Practices on the Safe Handling of Cytotoxic Drugs Among Oncology Nurses Working at Tertiary Teaching Hospitals in Addis Ababa, Ethiopia	Drug Healthc Patient Saf. 2021;13:71-80	10.2147/DHPS.S289025
[13]	Azari et al.	2016	Environmental monitoring of occupational exposure to cyclophosphamide drug in two Iranian hospitals	Int J Cancer Manag. 2017;10(1):e7229	10.17795/ijcp-7229
[14]	Benoist et al.	2022	Perception, knowledge and protective practices for surgical staff handling antineoplastic drugs during HIPEC and PIPAC	Pleura Peritoneum. 2022;7(2):77-86	10.1515/pp-2021-0151
[15]	Bernabeu-Martínez et al.	2021	Perception of risk of exposure in the management of hazardous drugs in home hospitalization and hospital units	PLoS One. 2021;16(7):e0253909.	10.1371/journal.pone.0253909
[16]	Bobin-Dubigeon et al.	2013	A new, validated wipe-sampling procedure coupled to LC-MS analysis for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination	J Anal Toxicol. 2013 Sep;37(7):433-9	10.1093/jat/bkt045
[17]	Boiano et al.	2014	Adherence to safe handling guidelines by health care workers who administer antineoplastic drugs	J Occup Environ Hyg. 2014;11(11):728-40	10.1080/15459624.2014.916809

[18]	Boiano et al.	2015	Adherence to Precautionary Guidelines for Compounding Antineoplastic Drugs: A Survey of Nurses and Pharmacy Practitioners	J Occup Environ Hyg. 2015;12(9):588-602	10.1080/15459624.2015.1029610
[19]	Claraz et al.	2020	Assessment of efficacy of postinfusion tubing flushing in reducing risk of cytotoxic contamination	Am J Health Syst Pharm. 2020; 77(22):1866-1873	10.1093/ajhp/zxaa357
[20]	Connor et al.	2010	Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers	J Occup Environ Med. 2010;52(10):1019-27	10.1097/JOM.0b013e3181f72b63
[21]	Constantinidis et al.	2011	Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals	Eur J Cancer Care (Engl). 2011;20(1):123-31.	10.1111/j.1365-2354.2009.01150.n.a.
[22]	Cotteret et al.	2020	External contamination of antineoplastic drug vials: an occupational risk to consider	Eur J Hosp Pharm. 2022 Sep;29(5):284-286	10.1136/ejhpharm-2020-002440
[23]	Crickman	2016	Chemotherapy Safe Handling: Limiting Nursing Exposure With a Hazardous Drug Control Program.	Clin J Oncol Nurs. 2017;21(1):73-78.	10.1188/17.CJON.73-78
[24]	Crul and Simons-Sanders	2018	Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies	J Oncol Pharm Pract. 2018;24(7):483-489	10.1177/1078155217704990
[25]	Dugheri et al.	2018	A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments	Arh Hig Rada Toksikol. 2018 Sep 1;69(3):226-237.	10.2478/aiht-2018-69-3125
[26]	Fernandes et al.	2016	Workplace Activity in Health Professionals Exposed to Chemotherapy Drugs: An Otoneurological Perspective	Int Arch Otorhinolaryngol. 2016;20(4):331-338.	10.1055/s-0036-1572431.
[27]	Forges et al.	2021	Evaluation of a safe infusion device on reducing occupational exposure of nurses to antineoplastic drugs: a comparative prospective study. Contamoins-1	Int Arch Occup Environ Health. 2021;94(6):1317-1325	10.1007/s00420-021-01679-x.
[28]	Fransman et al.	2014	Leukemia from dermal exposure to CP among nurses in the Netherlands: Quantitative assessment of the risk	Ann Occup Hyg. 2014 Apr;58(3):271-82.	10.1093/annhyg/met077

[29]	Ferron et al.	2015	Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey	Eur J Surg Oncol. 2015;41(10):1361-7.	10.1016/j.ejso.2015.07.012
[30]	Hon et al.	2011	Pilot evaluation of dermal contamination by antineoplastic drugs among hospital pharmacy personnel	Can J Hosp Pharm. 2011;64(5):327-32	10.4212/cjhp.v64i5.1067
[31]	Hon et al.	2011	Occupational Exposure to Antineoplastic Drugs: Identification of Job Categories Potentially Exposed throughout the Hospital Medication System	Saf Health Work. 2011;2(3):273-81	10.5491/SHAW.2011.2.3.273
[32]	Kieffer et al.	2015	Preventing the contamination of hospital personnel by cytotoxic agents: evaluation and training of the para-professional healthcare workers in oncology units	Eur J Cancer Care (Engl). 2015 (3):404-10	10.1111/ecc.12249
[33]	Kim et al.	2019	Korean nurses' adherence to safety guidelines for chemotherapy administration	Eur J Oncol Nurs. 2019;40:98-103	10.1016/j.ejon.2019.04.002
[34]	Koller et al.	2018	Environmental and biological monitoring on an oncology ward during a complete working week	Toxicol Lett. 2018;298:158-163	10.1016/j.toxlet.2018.05.002.
[35]	Kopp et al.	2013	Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings	International Archives of Occupational and Enviromental Health	10.1007/s00420-012-0742-z
[36]	Korczowska et al.	2020	Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries—results of the MASHA project	Eur J Oncol Pharm 2020; 3(2):p e24	10.1097/OP9.0000000000000024
[37]	Kumari et al.	2017	Potential Health Risks among Oncology Staff Nurses of Selected Hospitals due to Antineoplastic Drug Exposure	Indian J Public Health Res Dev 2017; 8(4): 358-361	10.5958/0976-5506.2017.00369.2
[38]	Ladeira et al.	2014	Assessment of genotoxic effects in nurses handling cytostatic drugs	Toxicol Environ Health A. 2014;77(14-16):879-87.	10.1080/15287394.2014.910158
[39]	Lalande et al.	2012	Evaluation of safe infusion devices for antineoplastic administration	J Infus Nurs. 2015;38 Suppl 6:S29-35	10.1097/NAN.0b013e3182659abd

[40]	Larroque et al.	2021	Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy	Toxicol Appl Pharmacol. 2021;429:115694	10.1016/j.taap.2021.115694
[41]	Leduc-Souville et al.	2013	Risk management of excreta in a cancer unit	Clin J Oncol Nurs. 2013 Jun;17(3):248-52.	10.1188/13.CJON.248-252
[42]	Liu et al.	2022	Nurses' knowledge, perceptions, and behaviors regarding antineoplastic drugs: the mediating role of protective knowledge	Front. Nurs. 202; 29(2), 3922,155-163.	10.2478/fon-2022-0017
[43]	Moretti et al.	2015	Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach	Int Arch Occup Environ Health. 2015;88(6):683-95.	10.1007/s00420-014-0993-y
[44]	Mucci et al.	2020	Occupational exposure to antineoplastic drugs in hospital environments: potential risk associated with contact with cyclophosphamide- and ifosfamide-contaminated surfaces	Med Pr. 2020;71(5):519-529.	10.13075/mp.5893.00931
[45]	Ndaw et al.	2018	Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination	Toxicol Lett. 2018;298:171-176.	10.1016/j.ton.a.let.2018.05.031
[46]	Rossignol et al.	2020	A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics	J. Pharmacol Toxicol Methods. 2020;101:106652	10.1016/j.vascn.2019.106652
[47]	Sadeghipour et al.	2013	Chemical contamination during the preparation of cytotoxics: validation protocol for operators in hospital pharmacies	J Oncol Pharm Pract. 2013;19(1):57-64	10.1177/1078155212452764
[48]	Sessink et al.	2011	Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device	J Oncol Pharm Pract. 2011;17(1):39-48	10.1177/1078155210361431

[49]	Siderov et al.	2010	Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device	J Oncol Pharm Pract. 2010 Mar;16(1):19-25	10.1177/1078155209352543
[50]	Sottani et al.	2010	An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers	J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(27):2593-605	10.1016/j.jchromb.2010.04.030
[51]	Sottani et al.	2012	Occupational exposure to antineoplastic drugs in four Italian health care settings	Toxicol Lett. 2012;213(1):107-15.	10.1016/j.ton.a.let.2011.03.027
[52]	Sugiura, et al.	2011	Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan	J Oncol Pharm Pract. 2011;17(1):20-8	10.1177/1078155210369851
[53]	Sugiura, et al.	2011	Risks to health professionals from hazardous drugs in Japan: A pilot study of environmental and biological monitoring of occupational exposure to CP	J Oncol Pharm Pract. 2011;17(1):14-9.	10.1177/1078155209358632
[54]	Ursini et al.	2019	Antineoplastic drug occupational exposure: a new integrated approach to evaluate exposure and early genotoxic and cytotoxic effects by no-invasive Buccal Micronucleus Cytome Assay biomarker	Toxicol Lett. 2019 Nov;316:20-26	10.1016/j.toxlet.2019.08.022
[55]	Viegas et al.	2018	Occupational exposure to cytotoxic drugs: the importance of surface cleaning to prevent or minimise exposure	Arh Hig Rada Toksikol. 2018;69(3):238-249.	10.2478/aiht-2018-69-3137
[56]	Viegas et al.	2014	Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals	Environ Monit Assess. 2014 Nov;186(11):7807-18.	10.1007/s10661-014-3969-1
[57]	Villarini et al.	2011	Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs	Mutagenesis. 2011 May;26(3):359-69.	10.1093/mutage/geq102

Period of the Study

While it is possible to clearly state the publication year for each of the considered studies, it is not possible to provide a trend about the study period - meant as the time span in which the surveys and/or the measurements of interest took place (Table 2). Roughly 48% of the reviewed articles do not provide sufficiently precise information on the time range, in terms of years in which the monitoring campaign took place. Regarding the remaining articles, considering five-year intervals from 1999 to 2022, a higher number of publications took place in the years between 2008 and 2012, showing a percentage of carried-out searches of 19%. It is followed closely by the 17% of studies taking place in the years from 2013 to 2017. Notably, some of the studies reported data from more than one of the identified periods. Based on our evidence, it's safe to affirm that at least 36% of the literature included in this systematic review is based on research performed in the decade from 2008 and 2017. These articles focus on the characterization of occupational exposure to ADs, the assessment of the associated risk and the staff's adherence to the prevention guidelines defined by the hospital. These may be inspired by the HDs lists by NIOSH published in 2004 and subsequently updated in 2010 and 2012.

Table S4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study period (five-year intervals). n.a.: information not available in the reviewed articles.

Study period	N (%)	References
2018 - 2022	5 (10%)	[12, 22, 40, 42, 44]
2013 - 2017	8 (17%)	[23 ,27, 29, 33, 34, 36, 45, 56]
2008 - 2012	9 (19%)	[16-18, 24, 32, 35, 41, 50, 51]
2003 - 2007	5 (10%)	[21, 24, 48, 50, 53]
1999 - 2002	3 (6%)	[24, 48, 50]
n.a.	23 (48%)	[10, 13-15, 19, 20, 25, 26, 28, 30, 31, 37, 38, 43, 46, 47, 49, 52, 54, 55, 57]

Geographical Distribution

Information about the geographical distribution is reported with an in-depth precision (Table 3): 29 of the reviewed studies (60%) are based in Europe, with most of them spread among France and Italy (21% and 17% respectively). It is interesting to see how Europe is the continent most involved in the study of occupational risk from ADs, while North America and Asia, in a first approximation, share the same degree of involvement in this field (12% and 10% respectively). Studies carried out in Europe show a more widespread application of new technologies in the medical field, such as PIPAC (Pressurized Intra Peritoneal Aerosol Chemotherapy) and HIPEC (Hyperthermic Intraperitoneal Chemotherapy) for the administration of ADs. They also suggest a deepening of knowledge among the personnel, following the application of guidelines, and experimentation of methods suitable for monitoring the contamination of places and surfaces in medical departments. The articles published in China, Japan and South Korea suggest the widespread goal of understanding the perception of risk by the medical personnel, and the potential risk influenced by the healthcare workers' knowledge of the guidelines and the application of the risk prevention methods. As for the studies published in North America and Australia, on more than one occasion they focus on the evaluation of risk reduction following the implementation of drug control programs and the use of the closed-system drug transfer device.

Table S5. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study location (major geographical areas). n.a.: information not available in the reviewed articles.

Study location	N (%)	References
Australia	1 (2%)	[49]
Brazil	1(2%)	[26]
Canada	2 (4%)	[30,31]
China	1 (2%)	[42]
Ethiopia	1 (2%)	[12]
Europe (multi-center study)	1 (2%)	[36]
France	10 (21%)	[10, 14, 16, 29, 32, 39-41, 45, 46]
Germany	2 (4%)	[34, 35]
Greece	1 (2%)	[21]
India	1 (2%)	[37]
Iran	1 (2%)	[13]
Italy	8 (17%)	[11, 25, 43, 44, 50, 51, 54, 57]
Japan	2 (4%)	[52, 53]
The Netherlands	2 (4%)	[24, 28]
Portugal	3 (6%)	[38, 55, 56]
South Korea	1 (2%)	[33]
Spain	1 (2%)	[15]
Switzerland	1 (2%)	[47]
U.S.A.	4 (8%)	[18, 20, 23, 48]
n.a.	4 (8%)	[17, 19, 22, 27]

Investigated Healthcare Structures

As, understandably, most of the reviewed studies being carried out within general hospital facilities, open for public access and service, three main categories of environments are considered in this study: (i) hospitals and university hospitals (71%), (ii) cancer treatment centres (10%) and other healthcare structures (13%). Notably, some of the study investigate more than one kind of this structure and some (15%) do not report detailed information on the type of healthcare structure in which the study was performed (Table 4.a). More in detail, speaking about these categories of healthcare structure, aware of the consistent lack of detailed description about the specific department investigated in the reviewed studies (around 65% of the studies do not provide clear information about this), most of the measurements within hospital structures involve the pharmacy department/drug-preparation unit (19%). Other main departments considered in studies under review are the administration units (8%), patient care units (4%) and hospital areas specifically used for the treatment of oncological pathologies (2%) (Table 4.b). Regarding the obtained results, it's interesting to observe how the study of environmental contamination is, understandably, mostly relegated to the medicines-preparation areas. However, this could be a limiting element as regards the contamination of shared areas in the hospital structure, with the possibility of putting at risk medical personnel who are not used – and consequently, unprepared – to the management of ADs.

Table S6. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to: a) Healthcare facilities considered in the studies under review. b) Departments and wards considered in the studies under review. n.a.: information not available in the reviewed articles.

Investigated environment		N (%)	Reference
a	Hospital or University Hospital	34 (71%)	[12-14, 19-21, 24-28, 30-39, 42-46, 48-50, 52-54, 56, 57]
	Cancer treatment centre/oncology hospital	5 (10%)	[16, 31, 36, 40, 52]
	Other	6 (13%)	[10, 11, 23, 39, 51, 55]
	n.a.	7 (15%)	[15, 17, 18, 22, 29, 41, 47]
b	Pharmacy and/or preparation units	9 (19%)	[22, 30, 46, 48-51, 54, 56]
	Administration units	4 (8%)	[33, 46, 54, 56]
	Patients care units	2 (4%)	[10, 51]
	Oncologic and/or other surgery units	1 (2%)	[45]
	Other	6 (13%)	[10, 28, 34, 35, 39, 53]
	n.a.	31 (65%)	[11-21, 23-27, 29, 31, 32, 36-38, 40-44, 47, 52, 55, 57]

References

1. Occupational Safety and Health Administration Guidelines for Cytotoxic (Antineoplastic) Drugs | Occupational Safety and Health Administration Available online: https://www.osha.gov/enforcement/directives/std-01-23-001 [Last Accessed on Aug 28, 2023].
2. OSHA - Occupational Safety and Health Administration Controlling Occupational Exposure to Hazardous Drugs Available online: https://www.osha.gov/hazardous-drugs/controlling-occex [Last Accessed on Aug 28, 2023].
3. NIOSH - National Institute for Occupational Safety & Health Preventing occupational exposure to antineoplastic and other drugs in healthcare settings; NIOSH - National Institute for Occupational Safety & Health, Ed.; Cincinnati, OH, 2008;
4. American Society of Health-System Pharmacists ASHP Guidelines on Handling Hazardous Drugs; American Society of Health-System Pharmacists, Ed.; 2006;
5. National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings; 2016;
6. United States Pharmacopeial Convention Hazardous Drugs – Handling in Healthcare Settings; 2017;
7. COMMISSION, E.; Directorate-General for Employment, S.A. and I.; Dialogue, D.E.. — W.C. and S.; Unit C.2— Health and Safety at Work, E.-O. Guidance for the safe management of hazardous medicinal products at work; EUROPEAN COMMISSION, 2023; ISBN ISBN 978-92-68-02978-7.
8. European Parliament and Counci Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work; 2022;
9. European Parliament and of the Council Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Art; 2004;
10. Acramel A, Fouque J, Blondeel-Gomes S, Huguet S, Rezai K, Madar O, Escalup L. Application of an Environmental Monitoring to Assess the Practices and Control the Risk of Occupational Exposure to Cyclophosphamide in Two Sites of a French Comprehensive Cancer Center. *Ann Work Expo Heal*. 2022, 66, 1215–1223.
11. Altini M, Bernabini M, Marchetti P, Orlando L, Rebesco B, Sirna V. Risk management of onco-hematological drugs: how and how fast can we improve? *Tumori*. 2016, 102, 15–29.
12. Asefa S, Aga F, Dinegde NG, Demie TG. Knowledge and Practices on the Safe Handling of Cytotoxic Drugs Among Oncology Nurses Working at Tertiary Teaching Hospitals in Addis Ababa, Ethiopia. *Drug Healthc Patient Saf*. 2021,13,71–80.
13. Azari, M.; Panahi, D.; Akbari, M.E.; Mirzaei, H.R.; Rezvani, H.R.; Zendehdel, R.; Mehrabi, Y.; Bayatian, M. Environmental Monitoring of Occupational Exposure to Cyclophosphamide Drug in Two Iranian Hospitals. Iran. J. Cancer Prev. 2017, 10, e7229.
14. Benoist, H.; Eveno, C.; Wilson, S.; Vigneron, N.; Guilloit, J.-M.; Morello, R.; Simon, N.; Odou, P.; Saint-Lorant, G. Perception, knowledge and protective practices for surgical staff handling antineoplastic drugs during HIPEC and PIPAC. Pleura and peritoneum 2022, 7, 77–86.
15. Bernabeu-Martínez, M.Á.; Sánchez-Tormo, J.; García-Salom, P.; Sanz-Valero, J.; Wanden-Berghe, C. Perception of risk of exposure in the management of hazardous drugs in home

hospitalization and hospital units. PLoS One 2021, 16, e0253909.

16. Bobin-Dubigeon C, Amiand M, Percheron C, et al. A new, validated wipe-sampling procedure coupled to LC-MS analysis for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination. *J Anal Toxicol.* 2013,37,433–439.

17. Boiano JM, Steege AL, Sweeney MH. Adherence to safe handling guidelines by health care workers who administer antineoplastic drugs. *J Occup Environ Hyg*. 2014, 11, 728–740.

18. Boiano JM, Steege AL, Sweeney MH. Adherence to Precautionary Guidelines for Compounding Antineoplastic Drugs: A Survey of Nurses and Pharmacy Practitioners. *J Occup Environ Hyg*. 2015, 12, 588–602.

19. Claraz P, Riff I, Vert C, et al. Assessment of efficacy of postinfusion tubing flushing in reducing risk of cytotoxic contamination. *Am J Heal Pharm*. A*JHP Off J Am Soc Hea. Pharm*. 2020,77,1866–1873.

20. Connor TH, DeBord DG, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med*. 2010,52,1019-1027.

21. Constantinidis TC, Vagka E, Dallidou, P, et al. Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals. *Eur J Cancer Care* (Engl). 2011,20, 123–131.

22. Cotteret C, Secretan P-H, Gilles-Afchain L, et al. External contamination of antineoplastic drug vials: an occupational risk to consider. *Eur J Hosp Pharm Sci Pract*. 2022,29,284–286.

23. Crickman R, Finnell DS. Chemotherapy Safe Handling: Limiting nursing exposure with a hazardous drug control program. *Clin J Oncol Nurs*. 2017,21,73–78.

24. Crul M, Simons-Sanders K. Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies. *J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract*. 2018,24,483–489.

25. Dugheri S, Bonari A, Pompilio I, Boccalon P, Mucci N, Arcangeli G. A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments. *Arh Hig Rada Toksikol*. 2018,69,226–237.

26. Fernandes NM, Pelissari IG, Cogo LA, Santos Filha VAV. Dos Workplace Activity in Health Professionals Exposed to Chemotherapy Drugs: An Otoneurological Perspective. I*nt Arch Otorhinolaryngol*. 2016,20,331–338.

27. Forges F, Blanc E, Raymond B, et al. Evaluation of a safe infusion device on reducing occupational exposure of nurses to antineoplastic drugs: a comparative prospective study. Contamoins-1. *Int Arch Occup Environ Health*. 2021,94,1317–1325.

28. Fransman W, Kager H, Meijster T, et al. Leukemia from dermal exposure to cyclophosphamide among nurses in The Netherlands: quantitative assessment of the risk. *Ann Occup Hyg*. 2014,58,271–282.

29. Ferron G, Simon L, Guyon F, et al. Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey. *Eur J Surg Oncol. J Eur Soc Surg Oncol Br Assoc Surg Oncol*. 2015,41,1361–1367.

30. Hon CY, Astrakianakis G, Danyluk Q, Chu W. Pilot Evaluation of Dermal Contamination by Antineoplastic Drugs among Hospital Pharmacy Personnel. *Can J Hosp Pharm*. 2011,64, 327–332.

31. Hon CY, Teschke K, Chua P, Venners S, Nakashima L. Occupational Exposure to Antineoplastic Drugs: Identification of Job Categories Potentially Exposed throughout the Hospital Medication System. *Saf Health Work*. 2011, 2, 273–281.

32. Kieffer C, Verhaeghe P, Lagrassa S, et al. Preventing the contamination of hospital personnel by cytotoxic agents: evaluation and training of the para-professional healthcare workers in oncology units. *Eur J Cancer Care* (Engl). 2015,24,404–410.

33. Kim O, Lee H, Jung H, Jang HJ Pang Y, Cheong H. Korean nurses' adherence to safety guidelines for chemotherapy administration. *Eur J Oncol Nurs. Off J Eur Oncol Nurs Soc*. 2019,40,98–103.

34. Koller M, Böhlandt A, Haberl C, Nowak D, Schierl R. Environmental and biological monitoring on an oncology ward during a complete working week. *Toxicol Lett*. 2018, 298,158–163.

35. Kopp B, Schierl R, Nowak D. Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings. *Int Arch Occup Environ Health*. 2013,86,47–55.

36. Korczowska E, Crul M, Tuerk J, Meier K. Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries—results of the MASHA project. *Eur J Oncol Pharm*. 2020,3.

37. Kumari S, Lobo DJ, Sequira L. Potential Health Risks among Oncology Staff Nurses of Selected Hospitals due to Antineoplastic Drug Exposure. *Indian J Public Heal. Res Dev* 2017,8,358–361.

38. Ladeira C, Viegas S, Pádua M, et al. Assessment of genotoxic effects in nurses handling cytostatic drugs. *J Toxicol Environ Health*. A 2014,77,879–887.

39. Lalande L. Galy G, Dussossoy E, Noyel J.-E, Pivot C. Evaluation of Safe Infusion Devices for Antineoplastic Administration. *J Infus Nurs. Off Publ Infus Nurses Soc*. 2015,38 Suppl6,S29-35.

40. Larroque M, Arnaudguilhem C, Bouyssiere B, et al. Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy. *Toxicol Appl Pharmacol*. 2021,429,115694.

41. Leduc-Souville B, Bertrand E, Schlatter J. Risk management of excreta in a cancer unit. *Clin J Oncol Nurs*. 2013,17,248–252.

42. Liu N, Lu H, Yi X.-Q, Yang Y, Huang X-H. Nurses' knowledge, perceptions, and behaviors regarding antineoplastic drugs: the mediating role of protective knowledge. *Front Nurs*. 3922,9,155–163.

43. Moretti M, Grollino MG, Pavanello S, et al. Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach. *Int Arch Occup Environ Health*. 2015,88,683–695.

44. Mucci N, Dugheri S, Farioli A, et al. Occupational exposure to antineoplastic drugs in hospital environments: potential risk associated with contact with cyclophosphamide- and ifosfamide-contaminated surfaces. *Med Pr*. 2020,71,519–529.

45. Ndaw S, Hanser O, Kenepekian, V, et al. Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination. *Toxicol Lett*. 2018,298,171–176.

46. Rossignol E, Amiand MB, Sorrieul J, Bard JM, Bobin-Dubigeon C. A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics. *J Pharmacol Toxicol Methods*. 2020,101,106652.

47. Sadeghipour F, Lorenzini KI, Ziewitz C, Dobrinas M, Fleury M, Bonnabry P. Chemical contamination during the preparation of cytotoxics: validation protocol for operators in hospital pharmacies. *J Oncol Pharm Pract. Off Publ Int. Soc Oncol Pharm Pract*. 2013,19,57–64.

48. Sessink PJM, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract. Off Publ Int. Soc Oncol Pharm Pract*. 2011,17,39–48.

49. Siderov J, Kirsa S, McLauchlan R. Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device. *J Oncol Pharm Pract. Off Publ Int. Soc Oncol Pharm Pract*. 2010,16,19–25.

50. Sottani C, Porro B, Comelli M, Imbriani M, Minoia C. An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers. J *Chromatogr B, Anal Technol Biomed. life Sci*. 2010,878,2593–2605.

51. Sottani C, Porro B, Imbriani M, Minoia C. Occupational exposure to antineoplastic drugs in four Italian health care settings. *Toxicol Lett*. 2012,213,107–115.

52. Sugiura S, Nakanishi H, Asano M, et al. Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan. *J Oncol Pharm Pract. Off Publ Int Soc Oncol Pharm Pract*. 2011,17 20–28.

53. Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T. Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide. *J Oncol Pharm Pract. Off Publ Int. Soc Oncol Pharm Pract*. 2011,17,14–19.

54. Ursini CL, Omodeo Salè E, Fresegna AM, et al. Antineoplastic drug occupational exposure: a new integrated approach to evaluate exposure and early genotoxic and cytotoxic effects by no-invasive Buccal Micronucleus Cytome Assay biomarker. *Toxicol Lett*. 2019,316, 20–26.

55. Viegas S, Oliveira de AC, Carolino E, Pádua M. Occupational exposure to cytotoxic drugs: the importance of surface cleaning to prevent or minimise exposure. *Arh Hig Rada Toksikol*. 2018,69,238–249.

56. Viegas S, Pádua M, Veiga AC, Carolino E, Gomes M. Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals. *Environ Monit Assess.* 2014,186,7807–7818.

57. Villarini M, Dominici L, Piccinini R, et al. Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs. *Mutagenesis* 2011, 26, 359–369.

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Mental Disorders Among Healthcare Students Attending a Large University Hospital in Milan, Italy

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Abstract

Background: *The high incidence rates, treatment difficulties, and tendency to become chronic, which subsequently affects personal and occupational functioning, make mental health disorders among the most important public health concerns. In this context, healthcare university students (HS) appear to be more vulnerable to psychological distress than others.* **Objective:** *Investigate the prevalence of diagnosed mental illness among different groups of HS to detect students who may be psychologically vulnerable and determine whether the implementation of support interventions is necessary.* **Methods:** *All HS who had a clinical examination performed by an occupational physician at our occupational health unit between 2021 and 2022 were included in our case series. Data were collected and analyzed as part of the occupational physicians' health surveillance program.* **Results:** *out of 679 HS (507 females, 172 males, aged 22.2±3.9 mean±s.d) undergone clinical examination at our Occupational Health Unit, 36 (5.3%) reported a diagnosed psychiatric illness, and 20 were receiving pharmacological therapy at the time of the visit. A higher prevalence of psychological disorders has been highlighted in females (6.1% vs 2.9% in males) and students of the mental health sector (11.1%) when compared with others. A fit-to-work judgment with prescription was necessary for 16.7% of students with mental diseases. The presence of psychiatric disorders was associated with underweight (27.8%) and higher smoking habit (44.4%).* **Conclusions:** *These results underline the necessity of improving the current health surveillance protocols, which should also evaluate students' psychological fragility and implement effective intervention strategies to promote their health and wellbeing.*

1. Introduction

The World Health Organization's definition of health includes not only physical but also mental and social well-being, introducing the idea of a holistic approach to health [1]. Due to their high incidence rates, treatment challenges, and propensity to become chronic, mental health disorders are one of the most significant public health issues [2].

It's known that the transition to university coincides with a critical period in the biological, psychological, and social development of students. Despite being a crucial transitional period, Literature reports few epidemiological studies about diagnosed mental health problems in college and university students [3]. Nonetheless, several studies examined the frequency of signs of psychological discomfort in university students, suggesting that 12-50% of

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university and college students meet the criteria for one or more common mental disorders [4-6]. A national survey in Norway reported a high prevalence of both mental health problems [7] and suicidal ideation and non-suicidal self-harm [8] among college and university students. Furthermore, there are some suggestions about the impact of the COVID-19 pandemic on college students' mental health, as evidenced by the rise in the number of students experiencing negative emotions and psychological issues during this period [9, 10].

In this context, there is significant evidence that healthcare students (HS) have high levels of mental discomfort and psychological distress with subsequent concerning effects on personal and occupational functioning [11]. A recent systematic review reported an estimated frequency of depression symptoms in medical students around the world at about 27.2% [12], while the global prevalence rate of anxious features among medical students was 33.8% [13]. Recent studies also highlighted a higher prevalence of sleep disorders in HS compared to the general population [14, 15], a critical issue in this population since sleep disorder symptoms may result in errors, accidents, or low academic performance [16]. During the COVID-19 pandemic, higher levels of anxiety, stress, and exhaustion were also reported in this category of university students [17].

There is evidence of a relationship between mental disorders and unhealthy lifestyle habits: a recent Italian study evaluated the cardiovascular risk in patients with mental illness compared to a control group. It highlighted that smoking habits were more common in people with mental problems (51.3%-64.7%) than control (20.4-25.9) [18]. Other studies showed that patients with mental illnesses are twice as affected by obesity, diabetes, and metabolic syndrome than the general population and, accordingly, are at increased risk of death due to cardiovascular disorders [19]. On the other hand, several mental diseases, including those in the "eating disorders" group, could be associated with underweight conditions, such as unhealthy and restricted nutrition habits with subsequent effects on the endocrine system [20], bone metabolism [21], and cardiovascular system [22].

The first aim of this study was to evaluate and compare the prevalence of diagnosed mental illness in different groups of HS at the start of their practical training to establish the necessity of implementing health surveillance programs with the intention of identifying and assisting students with psychological fragility. Secondarily, the study evaluated the correlation between mental disease and unhealthy lifestyle habits to identify the necessity of implementing health promotion programs in the student population.

2. Materials and Methods

Luigi Sacco University Hospital is part of the Italian public healthcare system. It has an agreement with the University of Milan, so resident doctors and numerous students attend its departments and clinics. According to Italian Law (Legislative Decree n. 81 of 2008, 9th April) [23], before beginning their training internship, all students are required to undergo a medical examination by an occupational physician to identify any health issues that could contraindicate the exposure to specific risk agents during the traineeship. A detailed medical history regarding past and present pathological conditions, chronic therapies, and lifestyle habits is part of the current health surveillance protocol. It also includes general clinical evaluation and specific clinical evaluation for the musculoskeletal system and blood chemistry tests aimed to determine susceptibility to exposure to biological agents and adequate vaccination coverage of the students. After the medical examination, the occupational physician issues a fitness-to-work judgment to protect the health and safety of the students, as well as all workers.

Our case series included all HS undergone clinical examination by an occupational physician at our Occupational Health Unit between 1st January 2021 and 31 December 2022. Presented data were collected and analysed as part of the health surveillance program carried out by the Occupational Health Unit. Data were presented as a whole and categorized by course of study. In particular, students were divided into 4 categories based on the study courses they had taken: medicine and surgery (MS), nursing (N), the mental health sector (MH, including

psychology students and psychiatric rehabilitation students), and other courses of study (O; including few students belonging to the courses of pharmacy, physiotherapy, orthoptists, and others not included in the previous groups). Resident doctors were not included in the study.

All data shown in our study were expressed as absolute numbers, percentages, and/or mean ± SD. The Student's t-test analysed between-group differences for the continuous variables, while categorical variables were analysed by the Fisher exact test. Differences in age, sex, and course of study were considered in data analysis. A p-value <0.05 was considered significant. Statistical analysis was performed with Microsoft Excel (Microsoft Office for Apple, "Office 365" Version) and R-Studio (*R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL:* https://www.R-project.org/).

3. Results

679 HS (507 females, 172 males, aged 22.2±3.9 mean±d.s.) underwent clinical examination by Occupational Physician at our Occupational Health Unit between the beginning of 2021 and the end of 2022. Out of them, 400 students (58.9%) attended MS, 107 (15.8%) N, 81 (12.0%) MH and 91 (13.3%) O.

As shown in Table 1, at the time of clinical examination, 72% of visited HS had a normal weight (body mass index - BMI - between 18 and 24,9 kg/m^2) while 13% suffered from underweight (BMI <18 kg/m^2) and 15% were overweight/obese (BMI > 24,9 kg/m^2). Smoking habit was referred by 19.1% of HS. At the time of the visit, 36 HS (5.3%) reported documentation related to a mental illness just diagnosed by a psychiatrist, and 20 of them (55.6%) were receiving pharmacological therapy. Out of these 36 HS, 47.2% suffered from anxiety, 30.6% had a diagnosis included in the "eating disorders" group (including anorexia nervosa, bulimia nervosa, and binge eating disorder), 13.9% suffered from depression, 5.6% had a positive clinical history for episodes of panic crisis, and 1 student was affected by delusional disorder.

Table 1. Demographic and clinical characteristics of the study population.

	Healthcare Students	
	n	**%**
Students		
All	679	100.0%
Females	507	74.7%
Males	172	25.3%
Age (years), mean±s.d.	22.2±3.9	
University Courses Attended		
Medicine and Surgery (MS)	400	58.9%
Nursing (N)	107	15.8%
Mental Health sector (MH)	81	12.0%
Other courses (O)	91	13.3%
BMI		
<18 kg/m^2	88	13.0%
18-24.9 kg/m^2	489	72.0%
25-30 kg/m^2	90	13.2%
>30 kg/m^2	12	1.8%
Smoking Habit		
Yes	130	19.1%
No	549	80.9%
Diagnosed Mental Illness		
Yes	36	5.3%
No	643	94.7%
Type of Psychiatric Disease (out of 36)		
Anxiety	17	47.2%
Eating disorders	11	30.6%
Depression	5	13.9%
Panic crisis	2	5.6%
Delusional disorder	1	2.7%
Fitness to Work Judgement		
Fit to work	671	98.8%
Fit to work with limitation or prescription	8	1.2%
Unfit to work	0	0.0%

Out of the overall population, in 98.8% of the cases, the Occupational Physician expressed a full fit to work judgment after the medical examination. In 1.2% of cases, a fit-to-work judgment with

Table 2. Clinical data and smoking habit: comparison between healthcare students with and without diagnosed mental diseases.

	No Mental Disorders n. (%)	Diagnosed Mental Disorders n. (%)	p
All (n. 679)	643 (100)	36 (100)	-
Females (n. 507)	476 (74.0)	31 (86.1)	0.11
Age (years)	22.1±3.9	24.1±4.1	0.002
BMI			
<18 kg/m²	78 (12.1)	10 (27.8)	0.02
18-25 kg/m²	466 (72.5)	23 (63.9)	0.26
>25 kg/m²	99 (15.4)	3 (8.3)	0.59
Smoking Habit	114 (17.7)	16 (44.4)	<0.001
Fitness to Work Judgement	**n. (%)**	**n. (%)**	**p**
Fit to work	641 (99.7)	30 (83.3)	-
Limitation or prescription	2 (0.3)	6 (16.7)	<0.001
Unfit to work	0	0	-

prescription was required: in two cases, specifically, a fit-to-work judgment was accompanied by recommendations regarding the exposure to biological risk in relation to student's increased susceptibility, and in eight cases, a close monitoring schedule for follow-up visits was indicated to track the development of the underlying disease throughout the student's internship.

When compared with students without psychiatric illness, students with mental diseases were older (24.1±3.9 y vs. 22.1±4 y, p=0.002), and the diagnosis of mental diseases, even if not significant, showed a higher prevalence in the women group (6.1%) than in men group (2.9%) (p=0.11). Related to life habits, when compared with students without mental disorders, in students with psychiatric diseases a higher prevalence of smoking habits (44.4% vs. 17.7%, p<0.001) and underweight (27.8% vs. 12.1%, p=0.02) were found. In 98.6% of the students without psychiatric illness, the Occupational Physician expressed a full fit to work judgment following the medical examination. In this group, a fit work judgment with prescriptions was required in two cases related to students' increased susceptibility to biological risk. Related to the group of students with psychiatric diseases a fit to work judgment with prescription was expressed by Occupational Physician in 16.7% of cases with the recommendation of a close monitoring schedule for follow-up visits to track the development of the underlying disease throughout the student's internship (Table 2).

Concerning the type of university course attended, a higher prevalence of psychiatric disorders was found in MH students than in other HS (11.1% vs 4.7%, p=0.02) (Figure 1). As shown in Figure 2, when compared with students attending other university courses, a higher prevalence of eating disorders (4.7%) and depression (3.7%) was found in MH students. In comparison, diagnosis of anxiety (3.2%) was more common in MS students.

4. Discussion

Healthcare settings can be a demanding workplace, with long and uncertain working hours, severe workloads, training competition, high responsibility, and continual exposure to suffering, illness, and death [24]. Increasing evidence in Literature shows that healthcare workers around the world report high levels of depression, anxiety, stress, burnout, and post-traumatic stress disorder [25]. In this context, it is crucial to identify, at an early phase, psychological fragility in order to put all the necessary precautions at work to safeguard the health and safety of

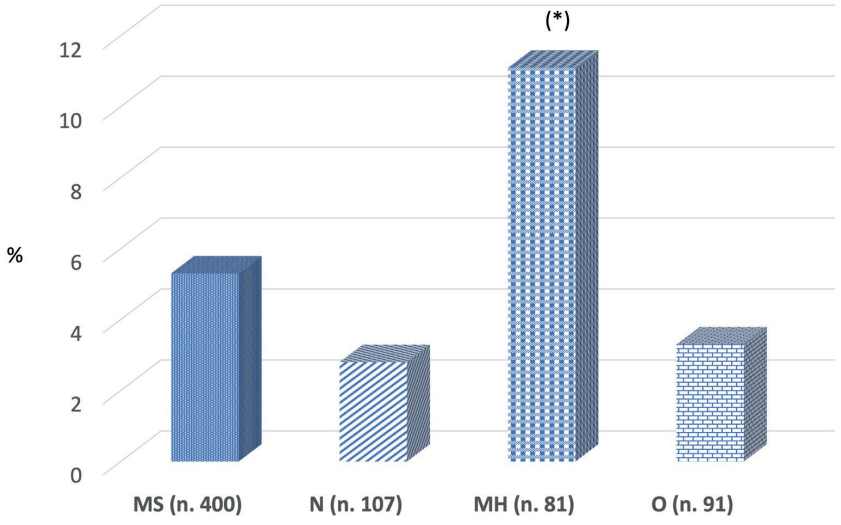

Figure 1. Prevalence of diagnosed mental disorders in study population categorized by university course attended.

MS = medicine and surgery course (n. 400), N = nursing course (n. 107), MH = mental health sector courses (n. 81), O = other courses (n. 91).

**p = 0.02.*

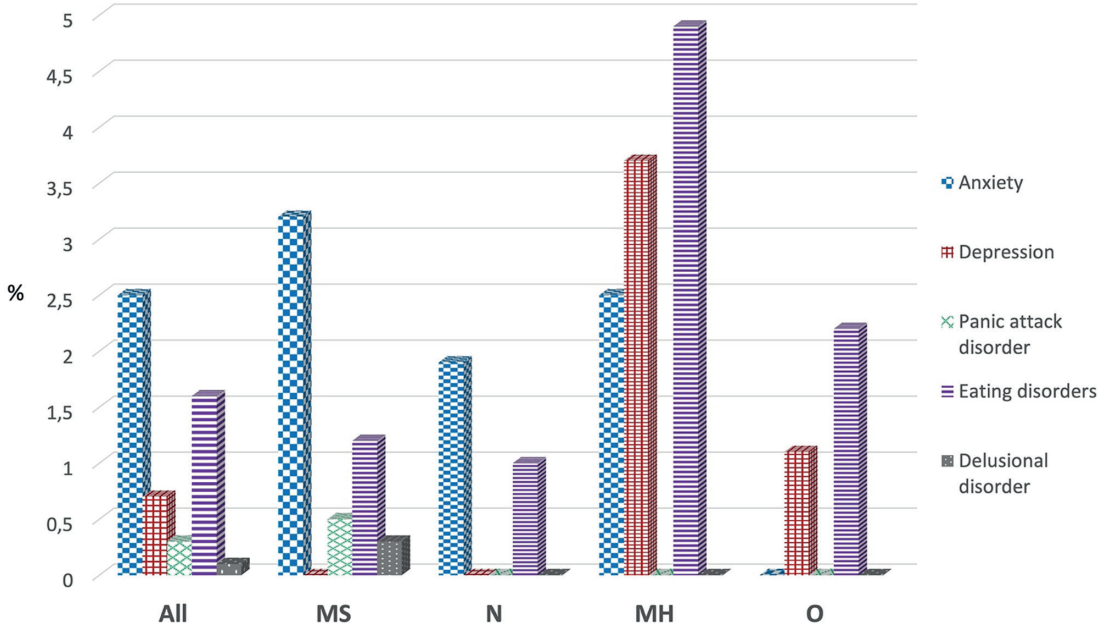

Figure 2. Prevalence of diagnosed psychiatric disease in the study population.

All = total of study population (n. 679), MS = medicine and surgery course (n. 400), N = nursing course (n. 107), MH = mental health sector courses (n. 81), O = other courses (n. 91).

workers, since from the university training period. Based on our knowledge, our study is the first in Literature to compare the prevalence of diagnosed mental illness in different groups of HS at the start of their practical training. In our study, out of 679 HS undergone to medical examination before the beginning of the Hospital practical training, 5.3% referred a diagnosed psychiatric illness at the time of the visit. Italian data [26] highlighted, for the general population with the same age range (18-34 y.o.), a prevalence of 1.3% of cases of psychiatric diseases requiring clinical evaluation during 2020; in the same survey, depression (0.3%), psychosis (0.3%) and anxiety/other neurotic syndrome (0.2%) were the most frequent diagnosis reported by 18-34 y.o. subjects undergone clinical evaluation. In our study, anxiety was the most frequent diagnosis reported (2.5% of the study population and almost half of psychiatric disease cases), while eating disorders affected 1.3% of visited students (almost one out of every three people with mental illness), and more then 10% of students with mental disease (and 0.7% of the study population) suffered from depression.

We found no research in Literature that investigated the prevalence of diagnosed psychiatric disorders in HS while several studies used standardized questionnaires to assess psychological well-being of this target population. A meta-analysis of ten cross-sectional studies, involving a total of 30,817 medical students, showed a prevalence of depression, anxiety, suicidal ideation, and eating disorders of 29%, 21%, 11%, and 2%, respectively [27]. Another study [28] assessed mental health status of college students and showed that anxiety was the prevalent psychological symptom in all groups (11.7-14.7%) followed by mood disorders (6.0-9.9%). The lack of targeted questionnaires in the assessment of psychological well-being of HS in our study could explain the lower prevalence of psychiatric discomfort in our population compared to other studies maybe because of an underestimation of cases due to the inability to recognize conditions of psychological suffering that have not yet been diagnosed and managed in a specialistic field. Our study highlighted older age in students with mental disorders compared to other students and a higher prevalence of psychiatric disease in women group than in men group. These findings are consistent with previous research works, which indicate that women have a higher prevalence of psychiatric illness than men [29, 30]. In relation to the finding of older age in our students with psychiatric disease, this data could be linked to the known effects of the underlying disorder on personal and work functioning [11]: several studies in Literature, in fact, have correlated the presence of psychological distress with delays in study path and lower academic performance [31, 32]. Concerning to the type of university course attended, in our study, a higher frequency of psychiatric disorders was found in students of MH sector than in other HS. Given the difficulty of comparing this data with the scientific Literature, lacking on this topic, we can hypothesize, based on our experience, that the Student's choice of academic course may also be influenced by their aim, on the one hand, to better understand their disorders and, on the other hand, to become able to help other people with the same kind of diseases.

In our study the Occupational Physician, after the medical examination, expressed a fit to work judgement with limitation/prescription in 16.7% of students with mental disorders compared to 1.4% of students without psychiatric disease. As previously reported, healthcare settings, characterized by high responsibility and continual exposure to suffering, illness, and death can be a demanding workplace [24]. Consequently, to manage a worker with psychiatric pathology, the Occupational Physician may need to provide a fit to work judgement with limitations or recommendations, specifically regarding working nights, workloads, responsibilities, and pace or a judgment of temporary or permanent unfitness depending on the severity of the medical condition [35]. Students attended in healthcare university courses at the start of their hospital internships made up our study population. All these students were expected to start an internship that was supervised, devoid of night shifts or direct responsibilities. Furthermore, students with psychiatric diseases involved in our study were all already taken care of by a specialist physician at the time of the visit and the specialist certified the status of good compensation for students with mental illness. For these reasons, even in presence of a psychiatric disease,

the Occupational Physician did not express an unfit to work judgement or a fit to work judgment with limitation to exposure to specific job risk in these cases. In 16.7% of students with psychiatric disease, a close monitoring schedule for follow-up visits and a close collaboration with the student's psychiatrist was established to track the development of the underlying disease throughout the student's internship.

Lastly, related to life habits, when compared with students without mental disorders, our results underlined that in students with psychiatric disease there was a higher prevalence of smoking habit, in line with data found in previous studies [18, 29]. Furthermore, unlike previous research that has linked psychiatric diseases to a higher frequency of overweight and obesity [19, 34], we discovered a substantial prevalence of underweight in our cohort of students with mental illness: this different finding could be due to the high prevalence, in our population, of eating disorders and subsequent restricted nutrition habit.

5. Conclusions

In conclusion, the high prevalence of mental disorders in our population compared to the general population, as well as the link between these disorders and unhealthy lifestyle habits, highlights the need to look at an improvement of the current health surveillance protocols that will also include an assessment of students' potential psychological fragility and subsequent effective intervention measures to support healthcare students' health and well-being (such as psychological interventions and stress management/reduction interventions).

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Author Contribution Statement: MM and PC conceived and designed the analysis; MM and FT collected the data; FT performed data mining; MM, FM and RC performed the analysis; MM, FM, RC, AS and SZ wrote the paper; PC supervised all phases of research activity planning. All authors reviewed the results and approved the final version of the manuscript.

References

1. Constitution of the World Health Organization. In: World Health Organization: Basic documents. 45th ed. Geneva: World Health Organization; 2005
2. Knapp M. Hidden costs of mental illness. *Br J Psychiatry*. 2003;183:477-478. Doi: 10.1192/bjp.183.6.477
3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in Arch Gen Psychiatry. 2005 Jul;62(7):768. Merikangas, Kathleen R [added]]. *Arch Gen Psychiatry*. 2005;62(6):593-602. Doi: 10.1001/archpsyc.62.6.593
4. Verger P, Guagliardo V, Gilbert F, Rouillon F, Kovess-Masfety V. Psychiatric disorders in students in six French universities: 12-month prevalence, comorbidity, impairment and help-seeking. *Soc Psychiatry Psychiatr Epidemiol.* 2010;45(2):189-199. Doi: 10.1007/s00127-009-0055-z
5. Eisenberg D, Hunt J, Speer N, Zivin K. Mental health service utilization among college students in the United States. *J Nerv Ment Dis.* 2011;199(5):301-308. Doi: 10.1097/NMD.0b013e3182175123
6. Blanco C, Okuda M, Wright C, et al. Mental health of college students and their non-college-attending peers: results from the National Epidemiologic Study on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2008;65(12):1429-1437. Doi: 10.1001/archpsyc.65.12.1429
7. Knapstad M, Sivertsen B, Knudsen AK, et al. Trends in self-reported psychological distress among college and university students from 2010 to 2018. *Psychol Med.* 2021;51(3):470-478. Doi: 10.1017/S0033291719003350.
8. Sivertsen B, Hysing M, Knapstad M, et al. Suicide attempts and non-suicidal self-harm among university students: prevalence study. *BJPsych Open*. 2019;5(2):e26. Doi: 10.1192/bjo.2019.4
9. Husky MM, Kovess-Masfety V, Swendsen JD. Stress and anxiety among university students in France during Covid-19 mandatory confinement. *Compr Psychiatry*. 2020;102:152191. Doi: 10.1016/j.comppsych.2020.152191
10. Li Y, Wang A, Wu Y, Han N, Huang H. Impact of the COVID-19 Pandemic on the Mental Health of College Students: A Systematic Review and Meta-Analysis. *Front Psychol*. 2021;12:669119. Doi: 10.3389/fpsyg.2021.669119
11. Dyrbye LN, Thomas MR, Shanafelt TD. Systematic review of depression, anxiety, and other indicators of psychological distress among U.S. and Canadian

medical students. *Acad Med*. 2006;81(4):354-373. Doi: 10.1097/00001888-200604000-00009
12. Rotenstein LS, Ramos MA, Torre M, et al. Prevalence of Depression, Depressive Symptoms, and Suicidal Ideation Among Medical Students: A Systematic Review and Meta-Analysis. *JAMA*. 2016;316(21):2214-2236. Doi:10.1001/jama.2016.17324
13. Quek TT, Tam WW, Tran BX, et al. The Global Prevalence of Anxiety Among Medical Students: A Meta-Analysis. *Int J Environ Res Public Health*. 2019;16(15):2735. Doi: 10.3390/ijerph16152735
14. Belingheri M, Luciani M, Ausili D, et al. Sleep disorders and night-shift work in nursing students: a cross-sectional study. *Med Lav*. 2022;113(1):e2022003. Doi: 10.23749/mdl.v113i1.12150
15. Belingheri M, Pellegrini A, Facchetti R, De Vito G, Cesana G, Riva MA. Self-reported prevalence of sleep disorders among medical and nursing students. *Occup Med (Lond)*. 2020;70(2):127-130. Doi: 10.1093/occmed/kqaa011
16. Gallego-Gómez JI, González-Moro MTR, González-Moro JMR, et al. Relationship between sleep habits and academic performance in university Nursing students. *BMC Nurs*. 2021;20(1):100. Doi: 10.1186/s12912-021-00635-x
17. Mittal R, Su L, Jain R. COVID-19 mental health consequences on medical students worldwide. *J Community Hosp Intern Med Perspect*. 2021;11(3):296-298. Doi: 10.1080/20009666.2021.1918475.
18. Salvi V, Aguglia A, Barone-Adesi F, et al. Cardiovascular risk in patients with severe mental illness in Italy. *Eur Psychiatry*. 2020;63(1):e96. Doi: 10.1192/j.eurpsy.2020.94
19. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls [published correction appears in World Psychiatry. 2018 Feb;17 (1):120]. *World Psychiatry*. 2017;16(2):163-180. Doi: 10.1002/wps.20420.
20. Baskaran C, Misra M, Klibanski A. Effects of Anorexia Nervosa on the Endocrine System. *Pediatr Endocrinol Rev*. 2017;14(3):302-311. Doi: 10.17458/per.vol14.2017.BMK.effectsanorexianervosa
21. Fazeli PK, Klibanski A. Effects of Anorexia Nervosa on Bone Metabolism. *Endocr Rev*. 2018;39(6):895-910. Doi: 10.1210/er.2018-00063
22. Casiero D, Frishman WH. Cardiovascular complications of eating disorders. *Cardiol Rev*. 2006;14(5):227-231. Doi: 10.1097/01.crd.0000216745.96062.7c
23. Legislative Decree n. 81 of 2008, 9th April. "Testo unico sulla salute e sicurezza sul lavoro" (available at: https://www.ispettorato.gov.it/documenti-e-normativa/normativa-di-interesse/salute-e-sicurezza-nei-luoghi-di-lavoro/; Last Access August 2023)
24. Perego G, Cugnata F, Brombin C, et al. The "Healthcare Workers' Wellbeing [Benessere Operatori]" Project: A Longitudinal Evaluation of Psychological Responses of Italian Healthcare Workers during the COVID-19 Pandemic. *J Clin Med*. 2022;11(9):2317. Doi: 10.3390/jcm11092317
25. Buselli R, Corsi M, Veltri A, et al. Mental health of Health Care Workers (HCWs): a review of organizational interventions put in place by local institutions to cope with new psychosocial challenges resulting from COVID-19. *Psychiatry Res*. 2021;299:113847. doi:10.1016/j.psychres.2021.113847
26. Italian Ministry of Health. "Mental health report 2020: data analysis from Mental Health Information System (SISM). Published in October 2021. (available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_3212_allegato.pdf; Last Access August 2023)
27. Zeng W, Chen R, Wang X, Zhang Q, Deng W. Prevalence of mental health problems among medical students in China: A meta-analysis. *Medicine (Baltimore)*. 2019;98(18):e15337. Doi: 10.1097/MD.0000000000015337
28. Auerbach RP, Mortier P, Bruffaerts R, et al. WHO World Mental Health Surveys International College Student Project: Prevalence and distribution of mental disorders. *J Abnorm Psychol*. 2018;127(7):623-638. Doi: 10.1037/abn0000362
29. Poirier MF, Canceil O, Baylé F, et al. Prevalence of smoking in psychiatric patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(3):529-537. Doi: 10.1016/s0278-5846(01)00304-9
30. Albert PR. Why is depression more prevalent in women? *J Psychiatry Neurosci*. 2015;40(4):219-221. Doi: 10.1503/jpn.150205
31. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014 [published correction appears in Sci Rep. 2022 Sep 1;12(1):14856]. *Sci Rep*. 2018;8(1):2861. Doi: 10.1038/s41598-018-21243-x
32. Kumar B, Shah MAA, Kumari R, Kumar A, Kumar J, Tahir A. Depression, Anxiety, and Stress Among Final-year Medical Students. *Cureus*. 2019;11(3):e4257. Doi: 10.7759/cureus.4257
33. Paro HB, Morales NM, Silva CH, et al. Health-related quality of life of medical students. *Med Educ*. 2010;44(3):227-235. Doi: 10.1111/j.1365-2923.2009.03587.x
34. Avila C, Holloway AC, Hahn MK, et al. An Overview of Links Between Obesity and Mental Health. *Curr Obes Rep*. 2015;4(3):303-310. Doi: 10.1007/s13679-015-0164-9
35. Elsayed YA, Al-Zahrani MA, Rashad MM. Factors affecting mental fitness for work in a sample of mentally ill patients. *Int J Ment Health Syst*. 2009;3(1):25. Doi: 10.1186/1752-4458-3-25.

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Original Article

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Risk of Skin Cancer in Workers Exposed to Diesel Exhaust: A Systematic Review and Meta-Analysis of Cohort Studies

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Keywords: Diesel Exhaust; Skin Cancer; Meta-analysis; Occupational Exposure; Occupational Health

Abstract

Background: *Our objective was to study the association between occupational exposure to diesel exhaust (DE) and skin cancer.* **Methods:** *A systematic review following STROBE guidelines and PECOS criteria was conducted to identify cohort studies describing the association between occupational DE exposure and the risk of skin cancer. We extracted 12 independent risk estimates for melanoma skin cancer (MSC), 8 for non-melanoma skin cancer (NMSC), and 3 for skin cancer not otherwise specified (SC-NOS). Random effects meta-analyses were performed, site-specific and stratified by geographic region and quality score. 95% confidence intervals (CI) were reported. Between-study heterogeneity and potential publication bias were investigated.* **Results:** *There was no overall evidence of an increased risk of MSC [RR=0.90, 95% CI: 0.73-1.11; I^2=92.86%, 95% CI: 82.83-97.03%], NMSC [RR=1.04, 95% CI: 0.88-1.23; I^2=60.79%, 95% CI: 0-87.34%] or SC-NOS [RR=0.72, 95% CI: 0.54-0.97; I^2=26.60%, 95% CI: 0-94.87%] in workers exposed to DE. No difference between low-quality and high-quality studies was found. A stratified analysis by geographical region did not reveal any significant differences. There was no evidence of publication bias.* **Conclusions:** *No evidence of an association between skin cancer and occupational DE exposure was found. Residual confounding and other sources of bias cannot be ruled out.*

1. Introduction

Diesel engines have many industrial applications, including on- and off-road equipment used in railroad, mining, construction, agriculture, transportation, and manufacturing operations [1]. The exhaust from diesel engines contains a mixture of gases, vapors, aerosols, and particulate matter that can create a health hazard when not properly controlled. Short-term exposure to high concentrations of diesel exhaust (DE) can cause eye, nose, throat, and lung irritation, headache, dizziness, coughing, phlegm, and nausea. In contrast, prolonged exposure can increase the risk of cardiovascular diseases, respiratory infections, and lung cancer.

In 2012, the International Agency for Research on Cancer (IARC) classified DE as a Group 1 carcinogen based on sufficient evidence in epidemiological studies that occupational exposure is associated with increased risk for lung cancer [2]. DE is also suspected to be linked to other cancers, including cancers of the bladder, larynx, hematolymphopoietic system, stomach, and ovary [3-6]. However, its carcinogenicity in humans has not yet been fully

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investigated since DE knowledge is relatively recent and based primarily on lung cancer studies [2].

Occupational risk factors for skin cancer include exposure to chemical carcinogens such as polycyclic aromatic hydrocarbons (PAH) and arsenic [7]. While there is also evidence in the scientific literature of an association between occupational exposure to ionizing and solar radiation and risk of skin cancer [8-10], it is not yet clear if DE exposure can also be considered an occupational risk factor for skin cancer.

This systematic review and meta-analysis aimed to investigate the association between occupational exposure to DE and the risk of all types of skin cancer (SC), including melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC).

2. Methods

2.1 Identification and Selection of Studies

We carried out a systematic review and reported it herein following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. The study protocol was registered in the PROSPERO database (Registration No. 352729). To be included in the systematic review, studies had to meet the criteria based on the elements of the review questions PECOS (Population, Exposure, Comparators, Outcomes, Study Design) [12].

The review was restricted to industrial cohort studies. We included all the publications cited in the most recent IARC Monograph on DE [1]. Two authors also independently searched the PubMed database to include all studies reporting results on occupational exposure to DE and risk of any type of cancer other than lung cancer, reported after IARC publication, for which a causal association with DE exposure has already been established. The search query used the string "(diesel OR miner OR garage OR railway OR ((truck OR bus) AND driver) OR (heavy equipment OR docker)) AND (cancer OR neoplasm)" to identify industry-based studies on cancer among workers exposed to DE. Reports found in the reference lists of the articles identified in the aforementioned steps were also used to complement the search. When several studies based on the same population were published, we only included the most insightful one (typically, the one that provided the largest number of cases or fatalities), and studies with modest overlap (i.e., less than 10%) were considered independent. Finally, we excluded research that did not mention DE exposure, had non-occupational exposure, lacked information on cancers other than lung cancer, and had a different design than cohort or case-control nested in the cohort.

2.2 Data Extraction

Data was collected and organized into predefined forms. The studies yielded the following information: (i) sociodemographic factors; (ii) occupation and industry type; (iii) person-years of observation; (iv) type of cancer – including ICD code with version; (v) measure of association – odds ratio (OR), risk ratio, rate ratio, standardized mortality ratio (SMR), or standardized incidence ratio (SIR), henceforth referred to as relative risk (RR), and 95% Confidence Intervals (CI); (vi) factors adjusted for in the analysis; (vii) characteristics of the study population (e.g., number of subjects included, number of cases). The dataset was then categorized based on the type of cohort study (historical or prospective), the duration of follow-up, geographic region, and the outcome (incidence or mortality). If available, we also gathered data on dose-response analysis for various indicators of DE exposure. However, there was insufficient information for the skin cancer meta-analysis to provide results related to dose-response or specific details regarding the type of DE exposure in the workplace.

2.3 Statistical Analysis

The quality assessment of the studies included in the meta-analysis was done independently by two authors (GC e FT) based on the CASP checklist. [13] The CASP assessment was based on 11 items for 14 points, and the final score was given by the mean of the results obtained by the two authors. A dichotomous variable for CASP assessment was then generated, considering studies that scored less

than 10 as "low quality" and those that scored 10 or more as "high quality".

A series of meta-analyses of non-overlapping studies were conducted to calculate pooled estimates with 95% CI for SC-NOS, MSC, and NMSC. Stratified meta-analyses by geographical region and quality score have also been performed. Further stratified analysis by outcome (incidence and mortality), sex, and industry type could not be conducted due to the small number of studies involved. The random-effects model described by Sidik and Jonkman was used for analysis. [14] RRs were reported with 95% CI, and p-value <0.05 was considered statistically significant. Additionally, we perform sensitivity analyses using multiple leave-one-out meta-analyses. Study heterogeneity was assessed using the inconsistency index (I^2 statistic and relative 95% CI [15]) with values of 0-30%, 31%-60%, 61%-75%, and 76%-100%, indicating low, moderate, substantial, and considerable heterogeneity, respectively [16]. Cochran's Q_b statistic for a test of group differences was used in the stratified analyses [17]. Finally, we assessed publication bias by performing the Egger test and by visually inspecting the funnel plots [18] and the Galbraith plots [19].

All the statistical analyses were performed on STATA, version 17.0 (Stata Corp., College Station, TX, US) [20]. Meta-analyses were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. PRISMA checklist is available in Table S1.

3. Results

3.1 Study Search and Study Characteristics

First, the systematic review comprised 19 papers that were included in the IARC monograph [2]. 2062 articles resulted from the PubMed literature search to include studies published after the IARC monograph's release. 1982 articles were excluded based on the publications' titles and abstracts, and 78 were excluded after reviewing the entire text. As a result, 9 non-overlapping reports found in the reference lists of the papers found in the previous steps were added to the review along with 2 new studies. A final number of 30 articles underwent full review, and 11 of them were included in the final analysis regarding skin cancer. Of those, 8 studies provided data on MSC (12 risk estimates), 5 for NMSC (8 risk estimates) and 3 for SC-NOS (3 risk estimates) (Figure 1). Six studies were performed in the United States, 3 in Sweden, and 1 each in Nordic countries combined, Canada, Denmark, and Finland. Further selected characteristics of the studies included in the review and meta-analysis are presented in Table 1.

3.2 Melanoma Skin Cancer

This meta-analysis included 7 studies, corresponding to 12 incidence risk estimates. The forest plot is shown in Figure 2. Overall, the risk of MSC was 0.90 (95% CI: 0.73-1.11). The leave-one-out meta-analysis revealed that no study had a larger influence on the estimation of the overall effect size than the others (Figure S1). The reported inconsistency index I^2 was 92.86% (95% CI: 82.83-97.03), indicating considerable heterogeneity [16]. The between-study variance τ^2 is estimated to be 0.08. The Egger test for publication bias was not significant (p=0.72). The corresponding funnel plot and Galbraith plot are reported in Figures S2 and Figure S3. Table 2 shows the results of the stratified analyses. No significant difference was detected between studies with a quality score greater or equal to 10 and those with a quality score less than 10 (Q_b=1.43; p=0.23). Stratified analysis by geographical region did not reveal any significant difference (Q_b=0.02; p=0.84).

3.3 Non-Melanoma Skin Cancer

This meta-analysis included 5 studies, corresponding to 8 incidence risk estimates. The forest plot is shown in Figure 2. Overall, the risk of NMSC was 1.04 (95% CI: 0.88-1.23). The leave-one-out meta-analysis revealed that no study had a larger influence on the estimation of the overall effect size compared with the others (Figure S4). The reported inconsistency index I^2 was 60.79% (95% CI: 0-87.34), indicating a moderate heterogeneity [16]. The between-study variance τ^2 is estimated to

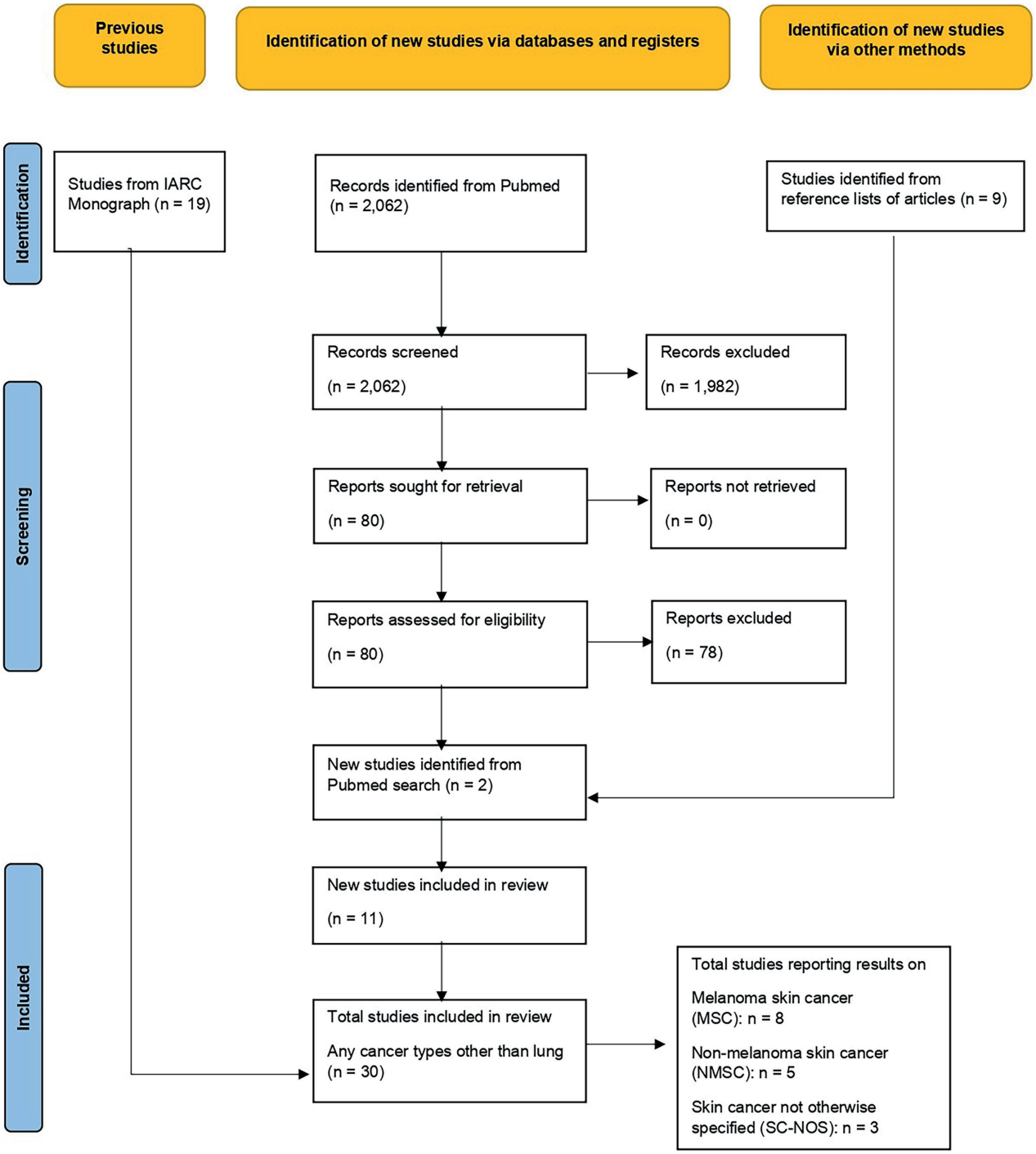

Figure 1. Flow diagram of the study selection process.

be 0.02. The Egger test for publication bias was not significant (p=0.65). The corresponding funnel plot and Galbraith plot are reported in Figures S5 and S6. Stratified analyses by geographical region could not be performed since all studies were conducted in Europe, while stratified analysis by quality score did not reveal any significant difference (Q_b=1.64; p=0.20).

Table 1. Selected characteristics of the studies included in the review and meta-analysis.

Study	Cancer Type	Country	Cohort Type	Follow-Up	Population	Person-years	Industry	Number of cases	Adjustments	CASP Assessment
[3]	MSC NMSC	Denmark	Retrospective Prospective	1943-92	16 023 men 1967 women	386 395	Bus drivers and tramway employers	MSC (Female): 11 MSC (Male): 255 NMSC (Female): 9 NMSC (Male): 219	-	9.5 – Low Quality
[21]	SC-NOS	Canada	Prospective	1965-77	43 826	290 186	Railroad	SC-NOS: 25	-	9 – Low Quality
[22]	SC-NOS	USA	Prospective	1964-78	34 156	372 525.6	Construction equipment operators	SC-NOS: 16	Age, calendar time	7.5 - Low Quality
[23]	MSC	USA	Prospective	1982-1987	461 981	939817	Railroad workers	MSC: 11	Sex, SES, smoking, BMI	10 – High Quality
[24]	MSC NMSC	Sweden	Prospective	1952-86 (mortality) 1958-84 (incidence)	695	21317.5 (mortality) 16695 (incidence)	Bus garage workers	MSC: 5 NMSC: 2	Occupational activity	9.75 – Low Quality
[25]	MSC	USA	Retrospective	1964-88	160 230	-	People of the KPMCP with self-reported exposure, no job or industry titles	MSC: 252	-	12 – High Quality
[26]	MSC NMSC	Finland	Retrospective	1953-91	212 800	8391	Locomotive drivers	MSC: 17 NMSC: 32	-	9 – Low Quality
[27]	MSC	Sweden	Prospective	1971-89	Employed Swedish adult population	Over 7640000 (exposed men) Over 240000 (exposed women)	Different job and industry titles (farmers excluded)	MSC (Female): 37 MSC (Male): 1272	-	11 – High Quality
[28]	MSC NMSC	Sweden	Prospective	1971-95	14364 Heavy construction equipment operators 6364 Truck drivers	-	(1) Heavy construction equipment operators (2) Truck drivers	MSC (1): 31 MSC (2): 14 NMSC (1): 28 NMSC (2): 19	Smoking	11.25 – High Quality
[29]	MSC NMSC	Denmark Finland Iceland Norway Sweden	Prospective	1961-2005	15 million (NOCCA cohort)	385 million	Engine operators	MSC (Female): 20 MSC (Male): 789 NMSC (Female): 16 NMSC (Male): 969	Age	12.75 – High Quality
[30]	SC-NOS	USA	Prospective	1989-2004	156 241	-	Truck drivers	SC-NOS: 30	Smoking	9.25 – Low Quality

SC-NOS: skin cancer not otherwise specified; MSC: melanoma skin cancer; NMSC: non-melanoma skin cancer; NEC: not elsewhere classified; SES: socio-economic status; BMI: body mass index; NOCCA: Nordic Occupational Cancer; KPMCP: Kaiser Permanente Medical Care Program.

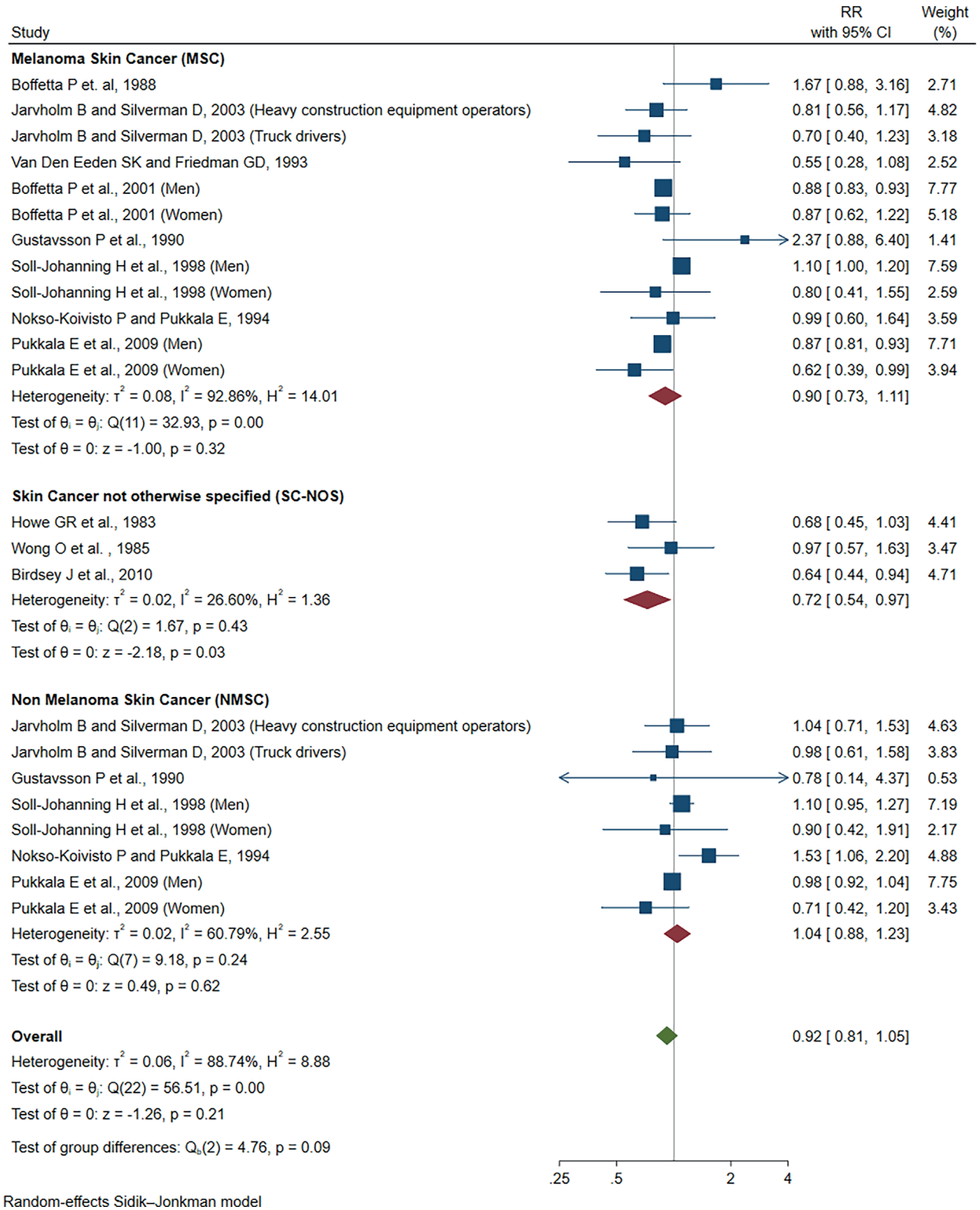

Figure 2. Forest plot of a meta-analysis of cohort studies on occupational exposure to diesel exhaust and skin cancer.

Table 2. Results of the metanalyses on the different skin cancers by geographic region and quality score.

Characteristic	Number of risk estimates	RR [95% CI]	Test of group Differences Q_b
MELANOMA SKIN CANCER (MSC)			
Geographic region			
North America	2	0.96 [0.34; 2.73]	0.02 (p = 0.84)
Europe	10	0.89 [0.74; 1.06]	
Quality score			
< 10	4	1.10 [0.73; 1.65]	1.43 (p = 0.23)
≥ 10	8	0.83 [0.67; 1.03]	
NON-MELANOMA SKIN CANCER (NMSC)			
Geographic region			
North America	-	-	-
Europe	8	1.04 [0.88; 1.23]	
Quality score			
< 10	4	1.18 [0.90; 1.54]	1.64 (p = 0.20)
≥ 10	4	0.96 [0.82; 1.13]	
SKIN CANCER – NOT OTHERWISE SPECIFIED (SC-NOS)			
Geographic region			
North America	3	**0.72 [0.54; 0.97]**	-
Europe	-	-	
Quality score			
< 10	3	**0.72 [0.54; 0.97]**	-
≥ 10	-	-	

3.4 Skin Cancer Not Otherwise Specified

This meta-analysis included 3 studies where the type of skin cancer was not specified, corresponding to 3 incidence risk estimates. The forest plot is shown in Figure 2. Overall, the risk of SC-NOS was 0.72 (95% CI: 0.54-0.97). The leave-one-out meta-analysis revealed that omitting the Howe GR et al. 1983 study [21] or the Birdsey J et al. 2010 study [30] causes the risk estimate to be no more significant (Figure S7). The reported inconsistency index I^2 was 26.60% (95% CI: 0-94.87). Even though the I^2 point estimate suggests low heterogeneity across the studies [16], the wide 95% confidence interval indicates substantial uncertainty around this estimate, suggesting that the true level of heterogeneity could potentially range from minimal to considerable. The between-study variance τ^2 is estimated to be 0.02. The Egger test for publication bias was not significant (p=0.20). The corresponding funnel plot and Galbraith plot are reported in Figures S8 and S9. Stratified analyses by geographical region and quality score could not be performed since all studies were conducted in North America and had a quality score lower than 10.

4. Discussion

This systematic review and meta-analysis of cohort studies investigated occupational exposure to DE and skin cancer risk. DE contains a complex mixture of chemicals, including PAHs and other potentially carcinogenic substances such as nitroarenes, benzene and formaldehyde, some of which have been linked to hyperkeratosis and dermatitis in humans [31-33], and to skin cancer in animal studies [34, 35].

Individuals with prolonged occupational exposure to DE, such as workers in industries like transportation or mining, may experience higher levels of skin contact with such substances. This prolonged and direct exposure could contribute to an increased risk of skin cancer since if carcinogens penetrate the skin barrier, they could potentially induce DNA damage or other cancer-promoting effects [36, 37]. Higher levels of PAH biomarkers have been detected in non-smoking workers exposed to DE and lubricating oil, suggesting the role of skin absorption in DE toxicology [38].

While we found no overall association between occupational DE exposure and skin cancer, an inverse relationship between occupational DE exposure and SC-NOS was suggested in site-specific analyses.

UV radiation is considered a skin carcinogen, which relates to work in the context of outdoor occupations [9]. However, we found evidence of a decreased risk of skin cancer in studies considering any type of SC-NOS. One might speculate that the reduced risk in workers exposed to DE might be related, for example, to the lack of solar exposure. It must be pointed out that we were not able to account for ultraviolet radiation exposure, and we did not have detailed information on the type of work activities of the populations of this meta-analysis, because the included studies did not report such data. Moreover, only 3 incidence risk estimates were available in studies with quality scores less than 10, limiting the power of the analysis. Also, the dispersion of true effect sizes addressed by the PI, which crossed the no-effect threshold, indicates that there are contexts where DE exposure has no effect or even an effect in the opposite direction on SC-NOS [15].

The importance of latency effects and other time-related factors, such as age at exposure, in determining cancer risk has long been acknowledged [39-40]. We restricted the meta-analysis to cohort studies since they provide higher-quality data and less opportunity for bias. This choice also resulted in the analysis of only long-term data, reducing the possibility of missing incident cases in the study populations.

It must also be pointed out that MSC and NMSC differ importantly in their epidemiology and known causes, and it is crucial to acknowledge and interpret the results with consideration to the distinct characteristics and risk factors associated with the two types of skin cancer. While UV exposure is a common risk factor for both types, MSC is often associated with intense, intermittent sun exposure, while NMSCs are linked to cumulative sun exposure [41, 42]. We decided however to combine them in a composite outcome, together with SC-NOS, for several reasons. First of all, pooling data from all three types of skin cancer increases the sample size, enhancing statistical power and the ability to detect significant associations. It also allows for a comprehensive examination of overall skin cancer risk, providing a more global view of the impact of DE. Finally, the focus of our analysis is on general skin cancer prevention and risk factors rather than specific cancer types.

4.1 Strengths and Limitations

This study has several strengths. To our knowledge, this is the first systematic review to investigate the association between occupational DE exposure and the risk of skin cancer. We focused on cohort studies since they provide higher-quality data compared to case-control or cross-sectional studies. Also, we focused on a specific working population that experiences higher levels of DE exposure than other working groups. Moreover, data collection included the working categories more likely to be exposed to DE. Regarding the statistical methods, we used the Random-Effects Sidik–Jonkman model [14] rather than the most popular DerSimonian–Laird method [43] due to the known tendency of the latter to underestimate the between-study variance τ^2 when the number of studies is small [44]. Finally, the meta-analysis was performed following solid methodological guidelines, considering the quality of the involved studies, and testing for possible publication bias.

However, the results should be interpreted cautiously, as some limitations should be acknowledged in addition to those inherent in meta-analyses. Firstly, the studies were heterogeneous in terms of the working population considered exposed, time period, and region of studies, and sample sizes were

variable. The small number of studies available for each meta-analysis also led to imprecise estimates of the heterogeneity, measured using the I^2 index. Further, we could not provide results by certain characteristics such as sex and industry type because data were insufficient, and only two studies adjusted for important confounders such as age. Secondly, differences in the definition of DE exposure and of the worker population involved might introduce misclassification, leading to bias in an unpredictable direction. Also, the lack of available dose-response data implied a limited ability to assess the association between DE exposure and skin cancer. A further important limitation is the lack of adjustment for major confounders, including solar radiation and chemical exposure. Moreover, the lack of studies conducted outside North America or Europe limits the global interpretability of the study results. Finally, as with all meta-analyses, publication bias cannot be ruled out entirely, given the low power of the relevant tests.

5. Conclusion

This study provided no evidence of an increased risk of skin cancer in workers exposed to DE. We did not identify patterns of risk that could be related to occupational DE exposure. The possibility of residual confounding and other sources of bias cannot be ruled out. Thus, additional investigations are required to understand better if an association between DE exposure and skin cancer exists.

Supplementary Materials: The following are available online:

- Table S1: PRISMA checklist
- Figure S1: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)
- Figure S2: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)
- Figure S3: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)
- Figure S4: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)
- Figure S5: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)
- Figure S6: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)
- Figure S7: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)
- Figure S8: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)
- Figure S9: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)

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Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

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Declaration of Interest: PB acted as expert witness in litigation concerning diesel exhaust exposure and gastrointestinal cancers, unrelated to the present work. No conflicts were reported by the other authors.

Author Contribution Statement: PB and GC conceived and designed the study; GC and FT searched the literature, identified relevant articles, and reviewed the full text, with PB assistance; MD conducted the statistical analysis and drafted the manuscript; GC and PB interpreted the data and revised the manuscript.

References

1. Pronk A, Coble J, Stewart PA. Occupational exposure to diesel engine exhaust: a literature review. *J Expo Sci Environ Epidemiol.* 2009;19(5):443-457. Doi: 10.1038/jes.2009.21
2. IARC: diesel engine exhaust carcinogenic. *Cent Eur J Public Health.* 2012;20(2):120, 138.

3. Soll-Johanning H, Bach E, Olsen JH, Tüchsen F. Cancer incidence in urban bus drivers and tramway employees: a retrospective cohort study. *Occup Environ Med*. 1998;55(9):594-598. Doi: 10.1136/oem.55.9.594
4. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, et al. Ovarian cancer and occupational exposures in Finland. *Am J Ind Med.* 1999;36(1):83-9. Doi: 10.1002/(sici)1097-0274(199907)36:1<83::aid-ajim12>3.0.co;2-q
5. Guo J, Kauppinen T, Kyyrönen P, et al. Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among finnish workers exposed to diesel or gasoline engine exhaust. *Int J Cancer.* 2004;111(2):286-92. Doi: 10.1002/ijc.20263
6. Andersen A, Barlow L, Engeland A, et al. Work-related cancer in the Nordic countries. *Scand J Work Environ Health.* 1999;25 Suppl 2:1-116.
7. Gawkrodger DJ. Occupational skin cancers. *Occup Med (Lond).* 2004;54(7):458-463. Doi: 10.1093/occmed/kqh098
8. Sena JS, Girão RJ, Carvalho SM, et al. Occupational skin cancer: Systematic review. *Rev Assoc Med Bras* (1992). 2016;62(3):280-286. Doi: 10.1590/1806-9282.62.03.280
9. Diepgen TL. Occupational skin diseases. *J Dtsch Dermatol Ges.* 2012;10(5):297-315. Doi: 10.1111/j.1610-0387.2012.07890.x
10. Karagas MR, Weinstock MA, Nelson HH. Keratinocyte Carcinomas (Basal and Squamous Cell Carcinomas of the Skin) In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. New York (US): Oxford University Press; 2006. p. 1230-50.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Published 2021 Mar 29. Doi: 10.1136/bmj.n71
12. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int.* 2018;121(Pt 1):1027-1031. Doi: 10.1016/j.envint.2018.07.015
13. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. Doi: 10.1136/bmj.n160
14. Sidik K, Jonkman JN. A simple confidence interval for meta-analysis. *Stat Med*. 2002;21(21):3153-9. Doi: 10.1002/sim.1262
15. Thorlund K, Imberger G, Johnston BC, et al. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. *PLoS One*. 2012;7(7):e39471. Doi: 10.1371/journal.pone.0039471
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-58. Doi: 10.1002/sim.1186
17. Cochran, WG. The comparison of percentages in matched samples. *Biometrika*. 1950;37(3-4):256-66.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-34. Doi: 10.1136/bmj.315.7109.629
19. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med*. 1988;7(8):889-94. Doi: 10.1002/sim.4780070807
20. StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.
21. Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ. Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J Natl Cancer Inst.* 1983;70(6):1015-9
22. Wong O, Morgan RW, Kheifets L, et al. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *Br J Ind Med.* 1985;42(7):435-48. Doi: 10.1136/oem.42.7.435
23. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med.* 1988;14(4):403-15. Doi: 10.1002/ajim.4700140405
24. Gustavsson P, Plato N, Lidström EB, Hogstedt C. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand J Work Environ Health.* 1990;16(5):348-54. Doi: 10.5271/sjweh.1780
25. Van Den Eeden SK, Friedman GD. Exposure to engine exhaust and risk of subsequent cancer. *J Occup Med.* 1993;35(3):307-11.
26. Nokso-Koivisto P, Pukkala E. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. *Occup Environ Med.* 1994;51(5):330-4. Doi: 10.1136/oem.51.5.330
27. Boffetta P, Dosemeci M, Gridley G, et al. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. *Cancer Causes Control.* 2001;12(4):365-74. Doi: 10.1023/a:1011262105972
28. Järvholm B, Silverman D. Lung cancer in heavy equipment operators and truck drivers with diesel exhaust exposure in the construction industry. *Occup Environ Med.* 2003;60(7):516-20. Doi: 10.1136/oem.60.7.516
29. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. *Acta Oncol.* 2009;48(5):646-790. Doi: 10.1080/02841860902913546
30. Birdsey J, Alterman T, Li J, et al. Mortality among members of a truck driver trade association. *AAOHN J.* 2010;58(11):473-80. Doi: 10.3928/08910162-20101018-01
31. Risher JF, Rhodes SW. Toxicological Profile for Fuel Oils. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); 1995 Jun.

32. Li FK, Yip PS, Chan KW, et al. Acute renal failure after immersion in seawater polluted by diesel oil. *Am J Kidney Dis.* 1999;34(6):E26. Doi: 10.1016/s0272-6386(99)70031-4
33. Barrientos A, Ortuño MT, Morales JM, et al. Acute renal failure after use of diesel fuel as shampoo. *Arch Intern Med.* 1977;137(9):1217.
34. Weistenhöfer W, Lutz R, Hiller J, Schmitz-Spanke S, Drexler H. Syncarcinogenesis of natural UV radiation and polycyclic aromatic hydrocarbons in the development of squamous cell carcinomas of the skin? *J Dtsch Dermatol Ges*. 2022;20(9):1179-1186. Doi: 10.1111/ddg.14818
35. National Toxicology Program. 15th Report on Carcinogens [Internet]. Research Triangle Park (NC): National Toxicology Program; 2021 Dec 21. Diesel Exhaust Particulates: CAS No.: none assigned. Available from: https://www.ncbi.nlm.nih.gov/books/NBK590901/
36. Stenehjem JS, Robsahm TE, Bråtveit M et al. Aromatic hydrocarbons and risk of skin cancer by anatomical site in 25000 male offshore petroleum workers. *Am J Ind Med*. 2017;60(8):679-688. Doi: 10.1002/ajim.22741
37. Kurtul S, Güngördü N. Occupational skin carcinogens. *Eur Res J.* 2023. Doi: 10.18621/eurj.1193815
38. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Diesel and Gasoline Engine Exhausts and Some Nitroarenes. Lyon (FR): International Agency for Research on Cancer; 2014. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 105.) 4. MECHANISTIC AND OTHER RELEVANT DATA. Available from: https://www.ncbi.nlm.nih.gov/books/NBK294271/
39. Solar and ultraviolet radiation. IARC Monogr Eval Carcinog Risks Hum. 1992;55:1-316.
40. Armenian HK. Incubation periods of cancer: old and new. *J Chronic Dis.* 1987;40 Suppl 2:9S-15S. Doi: 10.1016/s0021-9681(87)80004-8
41. Armstrong BK. How sun exposure causes skin cancer: An epidemiological perspective In: Hill D, Elwood JM, English D. Prevention of Skin Cancer. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2004. p. 89-116. Doi: 10.1007/978-94-017-0511-0_6
42. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. *Adv Exp Med Biol*. 2008;624:89-103. Doi: 10.1007/978-0-387-77574-6_8
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-88. Doi: 10.1016/0197-2456(86)90046-2
44. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods.* 2016;7(1):55-79. Doi: 10.1002/jrsm.1164

SUPPLEMENTARY MATERIAL

Table S1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pag. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pag. 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag. 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pag. 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pag. 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pag. 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pag. 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pag. 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pag. 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pag. 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pag. 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pag. 2-3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pag. 2-3

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pag. 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pag. 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pag. 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pag. 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pag. 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pag. 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Tab. 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tab. 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pag. 3-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups,	Pag. 3-9

Section and Topic	Item #	Checklist item	Location where item is reported
		describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pag. 3-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pag. 3-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pag. 3-9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pag. 9
	23b	Discuss any limitations of the evidence included in the review.	Pag. 10
	23c	Discuss any limitations of the review processes used.	Pag. 10
	23d	Discuss implications of the results for practice, policy, and future research.	Pag. 9-10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pag. 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pag. 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pag. 10
Competing interests	26	Declare any competing interests of review authors.	Pag. 11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pag. 10

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure S1. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)

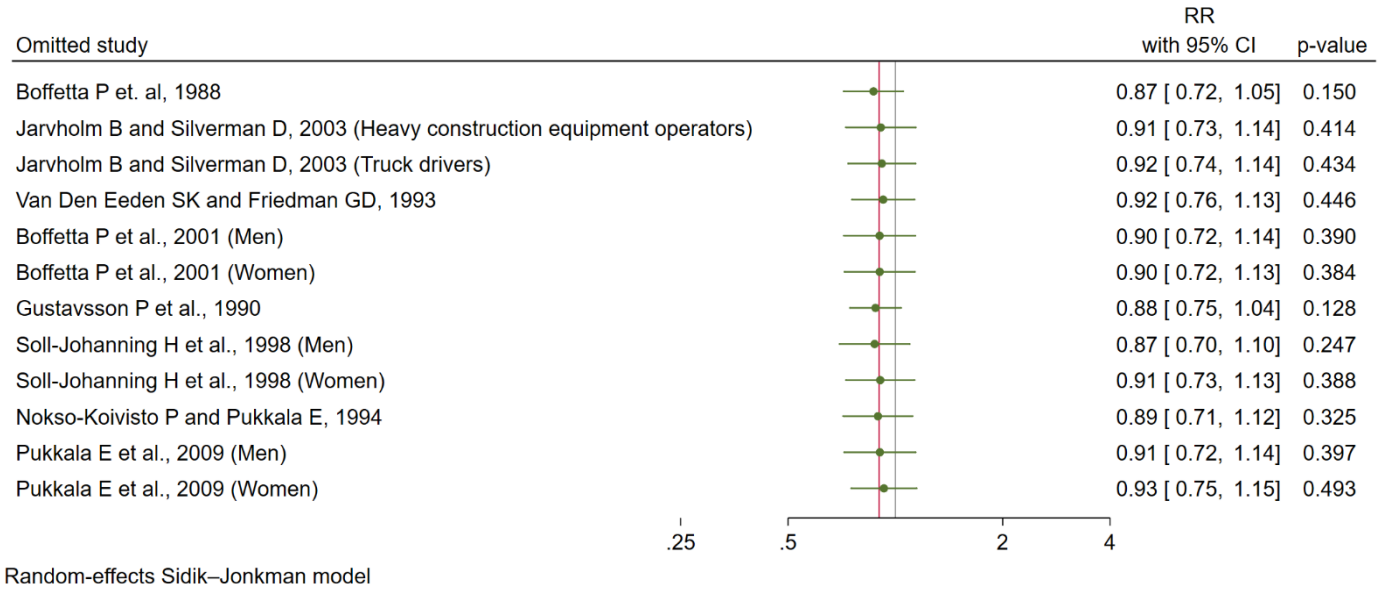


Figure S2. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)

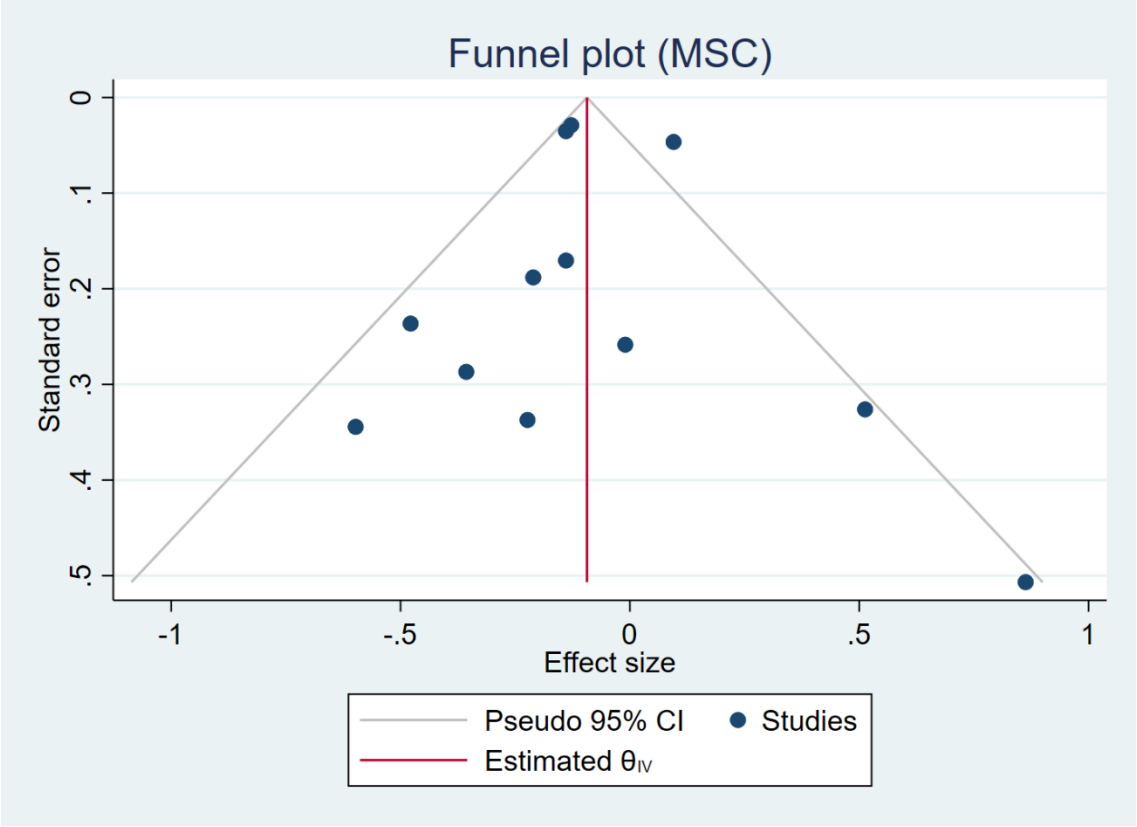


Figure S3. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of melanoma skin cancer (MSC)

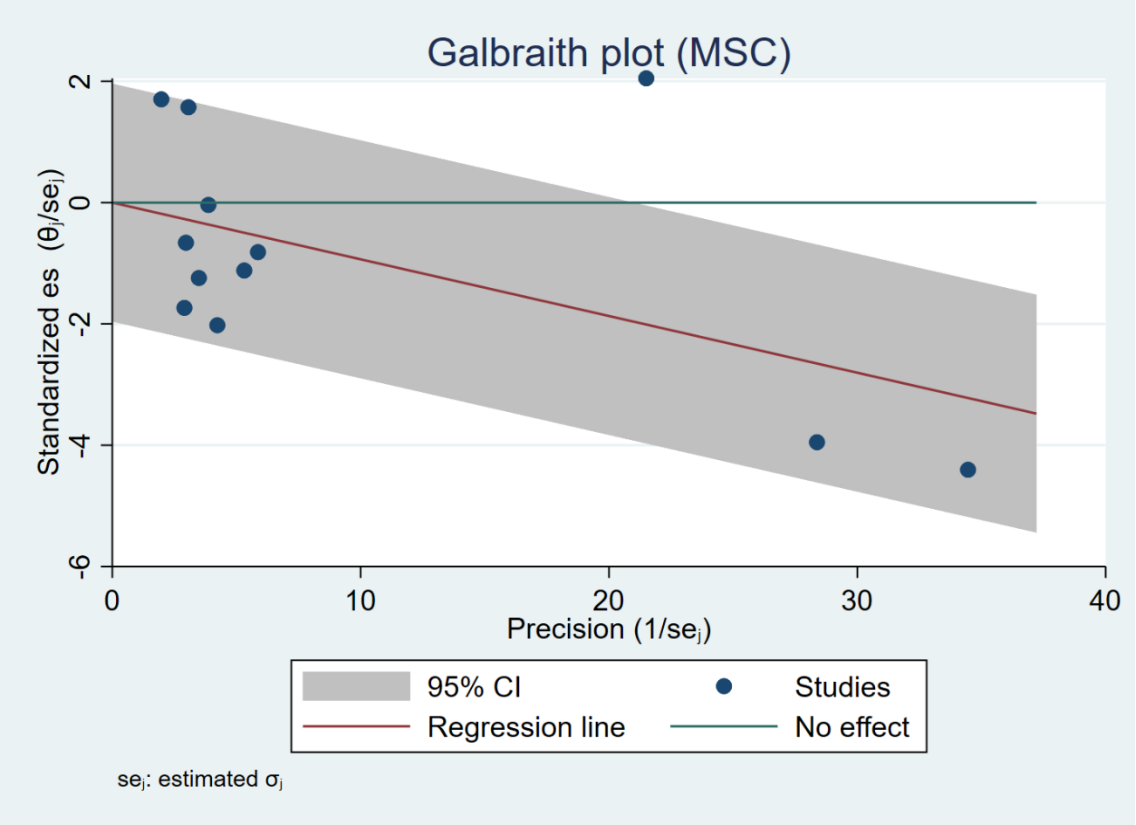


Figure S4. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)

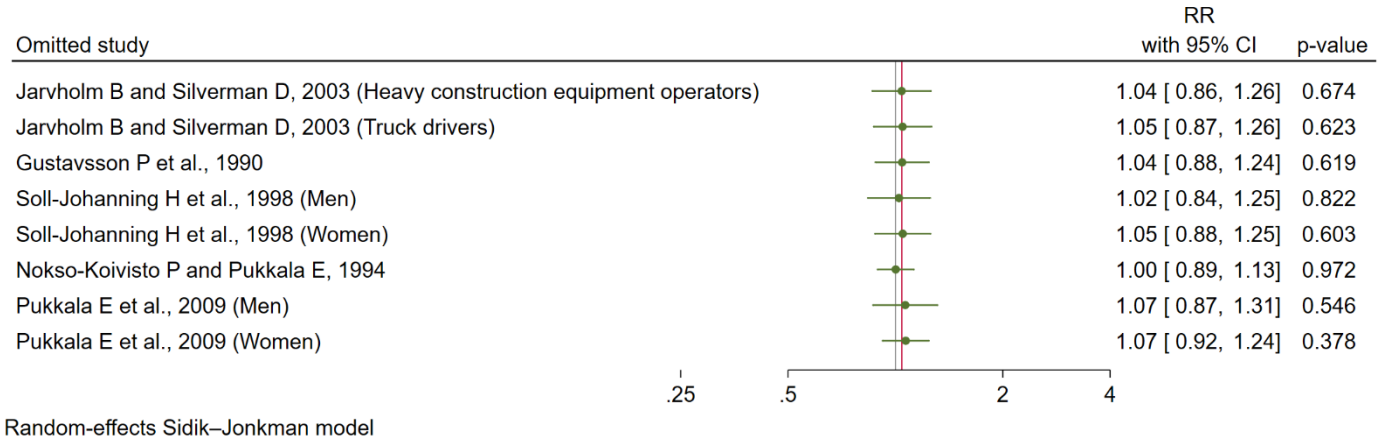


Figure S5. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)

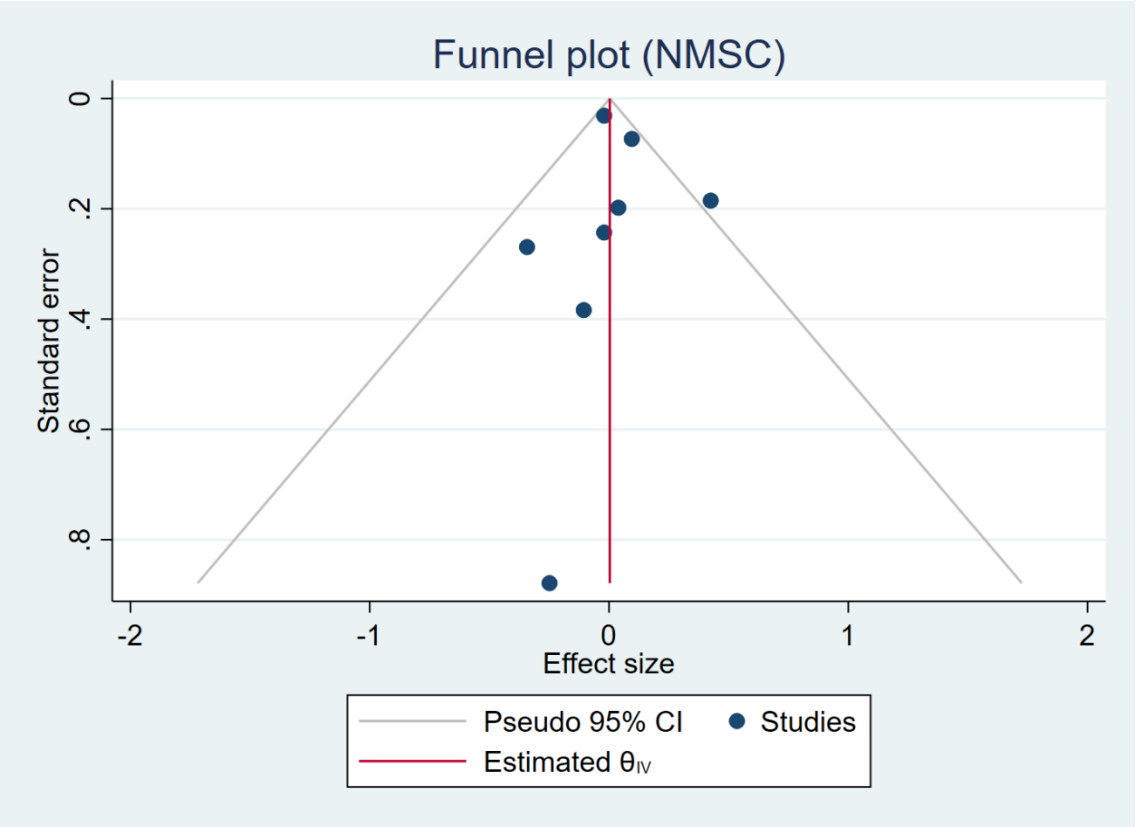


Figure S6. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of non-melanoma skin cancer (NMSC)

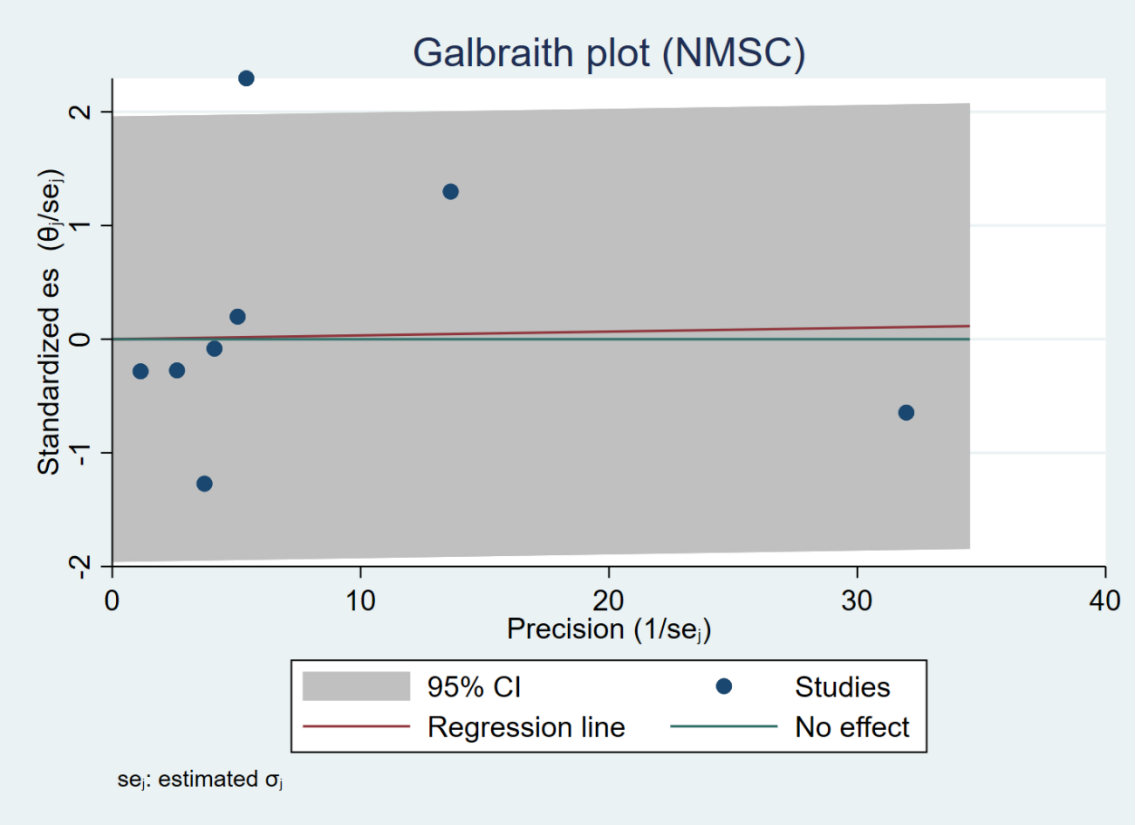


Figure S7. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)

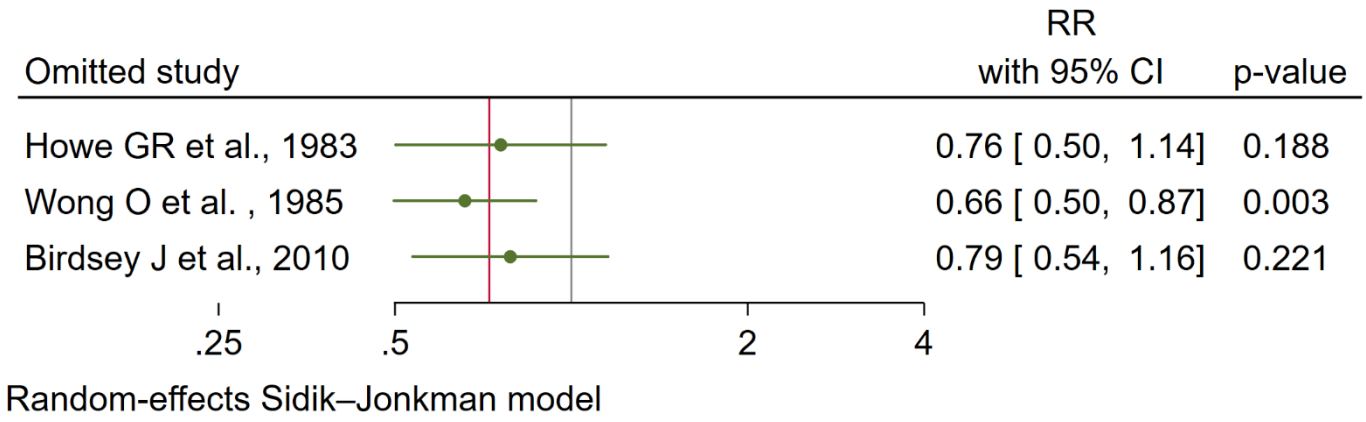


Figure S8. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)

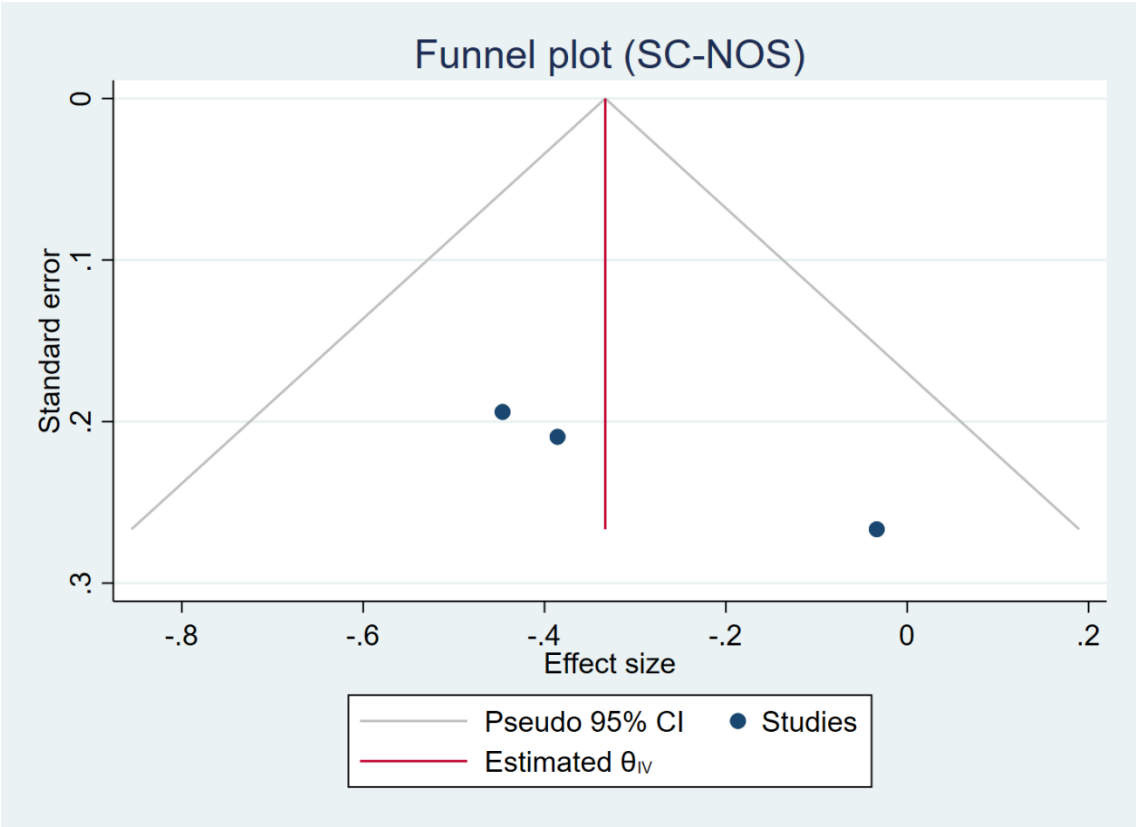
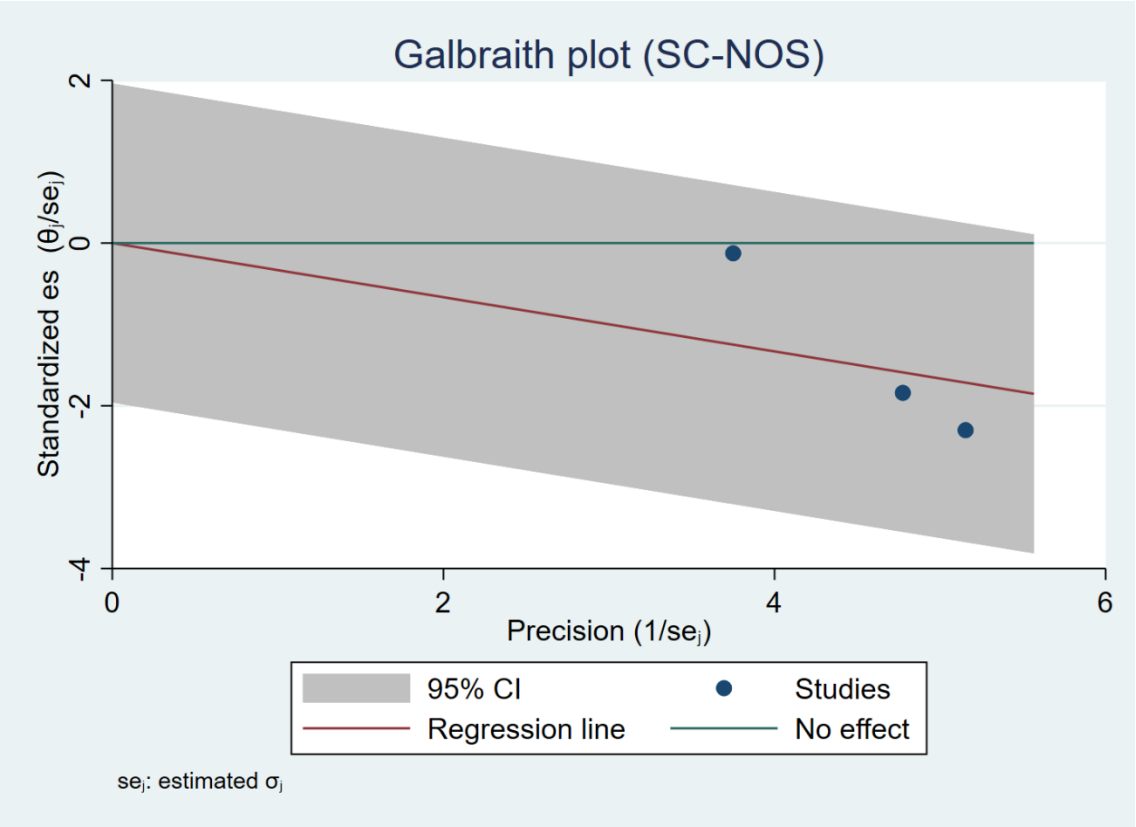


Figure S9. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of skin cancer not otherwise specified (SC-NOS)



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Cholangiocarcinoma and Occupational Exposure to Asbestos: Insights From the Italian Pooled Cohort Study

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Keywords: Cholangiocarcinoma; Asbestos Exposure; Cohort study; Cancer Registries

ABSTRACT

Background: *Recent studies supported the association between occupational exposure to asbestos and risk of cholangiocarcinoma (CC). Aim of the present study is to investigate this association using an update of mortality data from the Italian pooled asbestos cohort study and to test record linkage to Cancer Registries to distinguish between hepatocellular carcinoma (HCC) and intrahepatic/extrahepatic forms of CC.* **Methods:** *The update of a large cohort study pooling 52 Italian industrial cohorts of workers formerly exposed to asbestos was carried out. Causes of death were coded according to ICD. Linkage was carried out for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registries.* **Results:** *47 cohorts took part in the study (57,227 subjects). We identified 639 causes of death for liver and bile duct cancer in the 44 cohorts covered by Cancer Registry. Of these 639, 240 cases were linked to Cancer Registry, namely 14 CC, 83 HCC, 117 cases with unspecified histology, 25 other carcinomas, and one case of cirrhosis (likely precancerous condition). Of the 14 CC, 12 occurred in 2010-2019, two in 2000-2009, and none before 2000.* **Conclusion:** *Further studies are needed to explore the association between occupational exposure to asbestos and CC. Record linkage was hampered due to incomplete coverage of the study areas and periods by Cancer Registries. The identification of CC among unspecific histology cases is fundamental to establish more effective and targeted liver cancer screening strategies.*

1. Introduction

Cholangiocarcinoma (CC) is a malignant tumor that arises from biliary epithelium at any portion of the bile duct system and represents the second most common primary liver malignancy. CC are commonly divided into intrahepatic (ICC) and extrahepatic (ECC) forms (including perihilar and distal CC) [1]. These two forms differ in terms of risk factors, incidence and clinical presentation [2].

Although the incidence of ECC was stable or decreased in the last decades in Nordic Countries [3], an increase in the incidence of ICC was reported in the majority of countries worldwide [4]. In 2003-2017 in Italy, the average annual incidence rate for ICC was 1.8 and 1.1 per 100,000 person-years in

men and women, respectively [5]. In 2008-2012 in the same country, the age-standardised incidence rate of ICC was higher than ECC with a ratio of 1.2:1 [6].

In Italy, an increase of ICC mortality from 0.01 per 100,000 person-years in 1980 to 0.59 per 100,000 person-years in 2003 was reported [7]. In 2010-2014, age-standardised mortality rates from ICC reached the value of 1.00 per 100,000 person-years for men and 0.67 per 100,000 person-years for women [8]. Moreover, a slightly uptrend in survival from ICC has been reported in 2003-2017 [5]. With respect to ECC, mortality rates increased in the period 1980-1994, however a decreasing trend from 1995 to 2003 has been detected [7]. In 2010-2014, age-standardised mortality rates for ECC were 0.21 and 0.13 per 100,000 person-years in men and women, respectively [8].

Known/putative risk factors for CC include viral hepatitis B and C, liver fluke infections (e.g., *Clonorchis sinensis, Opistorchis viverrini*), primary sclerosing cholangitis, cholelithiasis/choledocholithiasis, hepatolithiasis, liver cirrhosis, non-alcoholic steatohepatitis, congenital/inherited conditions, personal habits like heavy alcohol consumption, cigarette smoking, and conditions such as obesity [9]. Despite this, in Western Countries about 50% of CC cases arise 'de novo' and no known risk factors are identified [10].

Recent cohort studies investigated the role of occupational exposure to chemical substances and risk of CC [11-13]. An increased risk for CC was found in printing workers exposed to 1,2-dichloropropane and/or dichloromethane [11-12].

The putative association of CC with occupational/environmental exposure to asbestos was investigated as well [14]. A case-control study reported a fourfold increased risk of ICC among ever exposed at work compared with never exposed (adjusted Odds Ratio [OR] 4.8, 95% Confidence Interval [95%CI] 1.7–13.3) [15]. Suggestive evidence that asbestos exposure might be associated with ECC was also observed [15]. A nested case-control study in the Nordic Occupational Cancer (NOCCA) cohort reported an increased risk of ICC with cumulative exposure to asbestos (≥15.0 f/mL × years vs never exposed: OR 1.7, 95%CI 1.1-2.6) [16]. Furthermore, a recent study carried out on ICC patients classified in small duct (sd-ICC) and large duct morphological subtypes (ld-ICC) suggested that sd-ICC might be more frequently associated to asbestos exposure than ld-ICC [17].

How asbestos inhaled or ingested fibres may reach the biliary tract is still an open question. It can be hypothesized that asbestos fibres might reach the bloodstream through the pulmonary and the portal lymphatic system [18-19]. In the liver, asbestos fibres might be trapped in Hering's channels and the terminal bile ductules, where they may cause direct damage on stem cell niche. At the same time, asbestos fibres may act indirectly, causing prolonged chronic inflammation in the same environment [20-21]. Of note, two recent studies detected the presence of asbestos fibres in the biliary tree/gallbladder and CC specimens of patients living in a highly polluted area [18, 22].

The aim of the present study is to investigate the association between occupational exposure to asbestos and risk of CC using an update of mortality data from the Italian pooled cohort study of workers formerly exposed to asbestos [23] and to test record linkage to Cancer Registries to distinguish between hepatocellular carcinoma (HCC) and ICC/ECC forms.

2. Methods

This study is based on the update of a large cohort study pooling 52 Italian industrial cohorts of former exposed to asbestos including a cohort of wives of asbestos cement workers and a cohort of Italian crocidolite miners in Australia [23]. In 2015, the pooled cohort study consisted of 43 cohorts mainly involved in asbestos cement industry, rolling stock construction and maintenance, and shipbuilding [24-29].

The update of the follow-up of the pooled cohort study was carried out based on the following steps: i) vital status and cause of death were ascertained through local Registrar's Offices; ii) in the case of decedents, local Registrar's Offices or Local Health Authority Registries of Causes of Death provided the cause of death, coded according to the International Classification of Disease (ICD, 8th, 9th and 10th revisions); and iii) the coordinating unit pooled the information of the different cohorts, including gender, date of birth, vital status, date of follow-up (either date of death for decedents or date

of the most recent observation for alive/lost subjects), cause of death for decedents, start/end date of each period of employment. For the different cohorts, the date of follow-up varied according to the most recent available update of mortality data and was comprised between 2018 and 2021 [23].

For the present study, we intended to identify those CC cases arising from the pooled cohort study in order to distinguish between HCC and CC and to further classify CC into ICC or ECC forms. Considering that the cause of death regarding liver/biliary tract neoplasms could be misclassified or classified with three-digit ICD codes, an attempt was made to perform a linkage for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registries. The linkage procedures were carried out by each Cancer Registry according to a deterministic approach based on the following variables: name, surname, date and place of birth. These procedures were performed for any subjects enrolled in the study independently of spatio-temporal coverage of Cancer Registry. Each Cancer Registry forwarded the anonymised data to the coordinating unit including date of incidence, morphology and topography code.

The study included the following causes of death coded according to ICD codes, namely: i) 155 (Malignant neoplasm of liver and intrahepatic bile ducts, specified as primary) and 156 (Malignant neoplasm of gallbladder and bile ducts) for ICD-8; ii) 155 (Malignant neoplasm of liver and intrahepatic bile ducts) and 156 (Malignant neoplasm of gallbladder and extrahepatic bile ducts) for ICD-9; and iii) C22 (Malignant neoplasm of liver and intrahepatic bile ducts), C23 (Malignant neoplasm of gallbladder), and C24 (Malignant neoplasm of other and unspecified parts of biliary tract) for ICD-10. Whereas possible, four-digit ICD codes were used.

The histological subtype groupings provided by Cancer Registries were based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes or earlier editions [30]. Cancer classification was made according to the European Network of Cancer Registries Recommendations [31].

For the present purpose, only a subset of cohorts established in an area covered by Cancer Registries were eligible for the study. In areas with no Cancer Registry coverage, a record linkage with hospital discharge records (HDR) was considered. This was the case of the three cohorts located in the province of Bologna, where the record linkage was performed using HDR classifying primary or concomitant diagnoses using ICD codes.

Standardized mortality ratios (SMR) were calculated according to causes of death for: i) liver and intrahepatic bile duct cancer; and ii) gallbladder and extrahepatic bile duct cancer [32]. For those cohorts included in the present study, workers contributed until their most recent date of observation. Age-, period-, sex-, region- and cause-specific rates were used as reference rates. Mortality rates for each region in which cohorts are located were used. The National Institute of Health (Istituto Superiore di Sanità, ISS) provided the set of rates based on mortality and population data (available since 1970) as supplied by the National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT). Consequently, analyses were restricted to person-years and events occurring after January 1st, 1970. Confidence intervals for SMRs were calculated according to the Poisson distribution of observed deaths at the 95% confidence value (95%CI) [32]. An alpha error of 0.05 was accepted. Analyses were carried out using OCMAP-plus cohort analysis program [33] and SAS 9.4 (SAS Institute Inc., USA).

3. Results

The update of the pooled cohort study consisted of 52 Italian industrial cohorts formerly exposed to asbestos. Of these, 47 participated in the study, including 44 cohorts established in an area covered by Cancer Registry and three located in the province of Bologna (i.e. Casaralta, Derbit, Officina Grandi Riparazioni). These 47 cohorts included 57,227 subjects (89.6% men, n=51,252). The description of the included cohorts along with Cancer Registries coverage is reported in Table 1. There is an overlap between cohorts and Registries, that is far from being complete both in time and in space. For instance, for Piedmont the largest cohorts (i.e. Eternit and wives of Eternit workers) were not located in an area covered by Cancer Registry. The vast majority of the

Table 1. Pooled Italian asbestos cohort study: description of the cohorts participating in the study.

Region	Company or cohort name	Location	Industrial Activity	Asbestos type	Year of activity	Total of subjects	Cancer Registry coverage (year of establishment)
Piedmont	Amiantifera [1,2]	Balangero	Miners	Chrysotile	1921-1989	974 men	Registry of Piedmont (1985): it covered only the city of Turin until 2007. Since 2008 the Registry has covered the province of Turin. Remaining provinces are not yet covered, but linkage was attempted because of internal migration and changes of residence. Incidence data were updated until 2019
	Eternit [3]	Casale Monferrato	Asbestos Cement	Chrysotile, crocidolite	1907-1986	3434 (2657 men)	
	Magliola	Santhià	Rolling stock maint and cons	Crocidolite, amosite	1901-1994	1563 (1415 men)	
	SACA [4]	Cavagnolo	Asbestos Cement	Chrysotile, crocidolite	1947-1982	869 (586 men)	
	SILA	Cigliano	Friction materials	Chrysotile	1924-active	421 (255 men)	
	Wives of Eternit workers [5]	Casale Monferrato	Wives workers	Chrysotile, crocidolite	1907-1986	1779 women	
Lombardy	Fibronit [6]	Broni	Asbestos Cement	Chrysotile, crocidolite, amosite	1932-1993	2012 (1841 men)	Registry of the province of Pavia: incidence data 2003 - 2018 were used
Liguria	Cantieri Navali Genoa [7]	Genoa	Shipyard	Mixed fibres	1933-active	3984 men	Registry of the province of Genova (1986): initially only the city, updated until 2016
Veneto	Compagnia Lavoratori Portuali	Venice	Harbour	Mixed fibres	1926-active	1956 (1954 men)	Registry of Region Veneto: the coverage has changed over the years. It covered the 27%, 33%, 45%, 49%, 53%, 96% and 100% of the population until 1987, 1988-1989, 1990-1997, 1998-2007, 2008-2012, 2013 and 2014-2018, respectively
	Edilit [8]	Vigodarzere	Asbestos Cement	Mixed fibres	1946-active	562 (339 men)	
	Fervet	Castelfranco Veneto	Rolling stock maint and cons	Crocidolite, amosite	1919-2008	970 (968 men)	
	Fincantieri	Venice	Shipyard	Mixed fibres	1940-active	4515 (4510 men)	
	Officine di Cittadella [9,10]	Cittadella	Rolling stock maint and cons	Mixed fibres	1946-2008	1255 (1244 men)	
	Officine Grandi Riparazioni FS	Vicenza	Rolling stock maint and cons	Mixed fibres	1919-active	1664 men	
	Officine Meccaniche Stanga [9,10]	Padua	Rolling stock maint and cons	Mixed fibres	1920-2008	2055 (2048 men)	

(*continued*)

Region	Company or cohort name	Location	Industrial Activity	Asbestos type	Year of activity	Total of subjects	Cancer Registry coverage (year of establishment)
Emilia-Romagna	Artclit [11]	Cadelbosco Sopra	Asbestos Cement	Chrysotile, crocidolite	1965-1988	55 (54 men)	Registry of the province of Reggio Emilia: incidence data from Jan 1, 1996 were used
	Cemental [11]	Correggio	Asbestos Cement	Chrysotile, crocidolite	1952-1989	562 (486 men)	
	Cemiant [11]	Cadelbosco Sopra	Asbestos Cement	Chrysotile	1968-1991	119 (28 men)	
	Fibrotubi [11]	Bagnolo in Piano	Asbestos Cement	Chrysotile, crocidolite	1957-1993	295 (237 men)	
	ICAR Eternit [11]	Rubiera	Asbestos Cement	Chrysotile, crocidolite	1961-1992	578 (510 men)	
	Itamiant [11]	Castelnovo Sotto	Asbestos Cement	Chrysotile, crocidolite	1955-1993	1216 (910 men)	
	Officine Gallinari	Reggio Emilia	Rolling stock cons	Mixed fibres	1957-1992	1682 (1664 men)	
	Sidercam [11]	Boretto	Asbestos Cement	Chrysotile, crocidolite	1969-1993	143 (131 men)	
	Uprocem [11]	Boretto	Asbestos Cement	Chrysotile, crocidolite	1973-1993	68 (52 men)	
	Maranit [11]	Poggio Renatico	Asbestos Cement	Chrysotile, crocidolite	1962-1993	202 (185 men)	Registry of the province of Ferrara (established in 1987): incidence data 1991-2011 were used
	Superlit [11]	Novi di Modena	Asbestos Cement	Chrysotile, crocidolite	1954-1993	174 (168 men)	Registry of the province of Modena (established in 1989): incidence data updated till 2015
	Casaralta [12]	Bologna	Rolling stock maint and cons	Crocidolite, amosite	1919-1998	1851 (1807 men)	No Registry covered the province of Bologna: incidence data reported in hospital discharge records (HDR) were used instead. HDR data were available since 1988 (exhaustive since 2004)
	Derbit [13]	Castenaso	Asphalt rolls	Chrysotile	1964-1997	410 (338 men)	
	Officina Grandi Riparazioni FS	Bologna	Rolling stock maint	Mixed fibres	1908-2018	3115 (3070 men)	

Tuscany	Baraclit	Bibbiena	Asbestos Cement	Chrysotile	1943-active	1029 men	Registry of Region Tuscany (established in 1985): incidence data for residents of Florence and Prato until 2013, and incidence data for the whole Region since 2013. Incidence data updated until 2017
	Borma	Leghorn	Glassworks	Mixed fibres	1900-1992	2422 (1947 men)	
	Breda [14]	Pistoia	Rolling stock cons	Mixed fibres	1918-active	3705 (3525 men)	
	Cantieri Navali Apuania	Massa Carrara	Shipyard	Mixed fibres	1949-active	920 (890 men)	
	Compagnia Lavoratori Portuali	Leghorn	Harbour	Mixed fibres	1957-active	2637 (2596 men)	
	Fervet	Viareggio	Rolling stock maint and cons	Chrysotile	1910-1993	876 (869 men)	
	Fibronit [15]	Avenza	Asbestos Cement	Chrysotile, crocidolite	1935-1985	262 (200 men)	
	Officine Grandi Riparazioni FS	Florence	Rolling stock maint and cons	Crocidolite, amosite	1930-2005	1001 men	
	Sacfem	Arezzo	Rolling stock cons	Crocidolite	1945-1983	692 (688 men)	
	Saivo	Florence	Glassworks	Chrysotile	1915-1992	1374 (1080 men)	
	Saline	Volterra	Rock salt workers	Chrysotile, amosite	1900-1992	489 (368 men)	
	Santa Lucia [16]	Pistoia	Industrial ovens cons	Chrysotile, crocidolite	1962-active	249 (233 men)	
	Signani	Aulla	Ship furniture	Mixed fibres	1945-1994	1338 (1314 men)	
	Siri	Sesto Fiorentino	Insulation	Mixed fibres	1951-1989	220 (219 men)	
	Veronit	Leghorn	Asbestos Cement	Chrysotile, crocidolite	1950-1989	159 (130 men)	
Sicily	Eternit	Syracuse	Asbestos Cement	Chrysotile, crocidolite	1953-1992	867 (608 men)	Registry of the province of Syracuse (1999)
	Sacelit [17,18]	San Filippo Mela	Asbestos Cement	Chrysotile, crocidolite	1958-1993	204 (177 men)	Registry of the province of Catania (2003)
Italy	Australian Blue asbestos [19]	Wittenoom (Australia)	Italian miners in Wittenoom	Crocidolite	1943-1967	300 (299 men)	Cancer Registry coverage according to residence

Abbreviations: Cons, construction; Maint, Maintenance. References related to cohorts included in the study are reported in Supplementary Table 1.

Table 2. Causes of death for liver and bile duct cancer in the 47 cohorts participating in the study (44 cohorts covered by Cancer Registry and three located in the province of Bologna) by calendar period.

	Causes of death for liver and bile duct cancer*							
	44 cohorts, N=639				3 cohorts, N=59			
	Cancer Registry, n (%)				**HDR, n (%)**			
	<2000	**2000-2009**	**2010-2019**	**Total**	**<2000**	**2000-2009**	**2010-2019**	**Total**
Cases identified by record linkage	73 (22.8)	83 (44.9)	84 (62.7)	240 (37.6)	5 (17.2)	12 (60.0)	3 (30.0)	20 (33.9)
Cases not identified by record linkage	247 (77.2)	102 (55.1)	50 (37.3)	399 (62.4)	24 (82.8)	8 (40.0)	7 (70.0)	39 (66.1)

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*
Abbreviations: HDR, Hospital Discharge Records.

included cohorts were involved in asbestos cement industry (n=19, 40.4%), rolling stock construction and maintenance (n=12, 25.5%), and shipyard/harbour (n=6, 12.8%). We identified 639 causes of death for liver and bile duct cancer in the 44 cohorts covered by Cancer Registry along with 59 cases identified in the three cohorts located in the province of Bologna (Table 2).

On the basis of the causes of death identified in the 47 cohorts, mortality for 'liver and intrahepatic bile duct cancer' did not increase (men: SMR 1.02, 95%CI 0.94-1.11; women SMR 0.98, 95%CI 0.68-1.35) as well as for 'gallbladder and extrahepatic bile duct cancer' (men: SMR 0.93, 95%CI 0.76-1.14; women: SMR 1.02, 95%CI 0.65-1.53).

Of the 639 causes of death referring to the 44 cohorts established in an area covered by Cancer Registry, 240 cases were identified by record linkage (Table 2). The proportion of cases identified by record linkage increased with Cancer Registry coverage 22.8% before 2000, 44.9% in 2000-2009, and 62.7% in 2010-2019. This was expected considering the increasing coverage of Cancer Registries as described in Table 1.

The site (topography) and the histology (morphology) of the 240 liver/biliary tract neoplasms linked to registry data were reported in Table 3.

Fourteen CC were identified, namely nine ICC, one ECC, one neoplasm involving both intrahepatic and extrahepatic bile ducts, and three cases not further classified. 83 HCC were present as well. In addition to that, we observed 117 cancers with unspecified histology (i.e. no morphology information available) and 25 carcinomas other than CC or HCC. Of note, one case of cirrhosis was identified (likely a precancerous condition considering that data retrieved from Cancer Registry were dated two months before the date of death). The classification of the 240 cases identified in the 44 cohorts covered by Cancer Registry according to ICD-O and calendar period is reported in Table 4.

No cases of CC were reported before 2000. Two ICC were identified in 2000-2009, while seven ICC, one ECC and four CC were reported in 2010-2019. The proportion of HCC was about one-third across the three time periods.

The description of the 14 cases of CC identified in the 44 cohorts covered by Cancer Registry is reported in Table 5.

These 14 cases of CC were characterised by: i) mean age of 72.9±10.7 years (range 58-89); ii) average of time since first exposure (TSFE) of 45.4±10.7 years (range 30-70); and iii) mean duration of exposure of 18.1±8.6 years (range 2-34). Out of 14 cases, 13 were men. A subgroup of 21 cases with unspecified histology and with topography codes referring to bile ducts showed the same characteristics as those experienced by these 14 CC cases (Supplementary Table 2). In the three cohorts established in the province of Bologna, we identified 59 causes of death for liver and bile duct cancer (Table 2). Of these, 20 cases were linked to HDR data (either as primary or concomitant disease). The description of the findings is reported in Table 6.

Table 3. Causes of death for liver and bile duct cancer identified by record linkage in the 44 cohorts covered by Cancer Registry (N=240).

Causes of death*	Cases identified by Cancer	ICD-O			
ICD-9	**Registry Linkage, n (%)**	**Morphology code**	**Topography code**	**Classification**	**n**
155-Malignant neoplasm of liver and intrahepatic bile ducts	40 (16.7)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	26
			C22.1-Intrahepatic bile duct	Unspecified	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	13
155.0-Malignant neoplasm of liver, primary	62 (25.8)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	22
			C22.1-Intrahepatic bile duct	Unspecified	1
		8001/3-Malignant tumor cells	C22.0-Liver	Unspecified	2
			C48.2-Peritoneum, NOS	Unspecified	1
			-	Unspecified	1
		8140/3-Adenocarcinoma	C22.0-Liver	Other ca.	1
			C18.9-Colon, NOS	Other ca.	1
			C80.9-Unknown primary site	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	29
			-	HCC	2
		-	C22.0-Liver	Cirrhosis	1
155.1-Malignant neoplasm of intrahepatic bile ducts	4 (1.7)	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	Unspecified	2
			C24.0-Extrahepatic bile duct	Unspecified	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
155.2-Malignant neoplasm of liver, not specified as primary or secondary	21 (8.8)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	8
			C18.9-Colon, NOS	Unspecified	1
			C38.4-Pleura, NOS	Unspecified	1
		8001/3-Malignant tumor cells	C22.0-Liver	Unspecified	1
		8010/3-Malignant epithelial tumor	C18.0-Cecum	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	9
156-Malignant neoplasm of gallbladder and extrahepatic bile ducts	4 (1.7)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
			C24.1-Ampulla of Vater	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	1

(*continued*)

Causes of death*	Cases identified by Cancer	ICD-O			
ICD-9	**Registry Linkage, n (%)**	**Morphology code**	**Topography code**	**Classification**	**n**
156.0-Malignant neoplasm of gallbladder	10 (4.2)	8000/3-Malignant tumor	C23.9-Gallbladder	Unspecified	2
		8010/3-Malignant epithelial tumor	C23.9-Gallbladder	Other ca.	1
		8090/3-Basal cell carcinoma, NOS	C44.5-Skin of trunk	Other ca.	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	5
		8480/3-Mucinous adenocarcinoma	C23.9-Gallbladder	Other ca.	1
156.1-Malignant neoplasm of extrahepatic bile ducts	5 (2.1)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	1
			C24.0-Extrahepatic bile duct	Unspecified	1
		8010/3-Malignant epithelial tumor	C23.9-Gallbladder	Other ca.	1
		8140/3-Adenocarcinoma	C24.0-Extrahepatic bile duct	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
156.2-Malignant neoplasm of ampulla of Vater	1 (0.4)	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	Unspecified	1
156.9-Malignant neoplasm of biliary tract, unspecified site	7 (2.9)	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	Unspecified	5
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
			C24.9-Biliary tract, NOS	Other ca.	1
ICD-10					
C22-Malignant neoplasm of liver and intrahepatic bile ducts	1 (0.4)	8000/3-Malignant tumor	C25.0-Head of pancreas	Unspecified	1
C22.0-Liver cell carcinoma	32 (13.3)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	11
		8010/3-Malignant epithelial tumor	C22.0-Liver	HCC	2
		8130/2-Papillary transitional cell carcinoma	C67.9-Bladder, NOS	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	18

C22.1-Intrahepatic bile duct carcinoma	11 (4.6)	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	Unspecified	1
			C24.9-Biliary tract, NOS	Unspecified	2
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.0-Liver	CC	1
			C22.1-Intrahepatic bile duct	ICC	5
			C24.0-Extrahepatic bile duct	ECC	1
			C24.9-Biliary tract, NOS	CC	1
C22.9-Malignant neoplasm of liver, not specified as primary or secondary	27 (11.3)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	14
			C22.1-Intrahepatic bile duct	Unspecified	1
			C26.9-Gastrointestinal tract, NOS	Unspecified	1
		8140/3-Adenocarcinoma	C22.0-Liver	Other ca.	1
			C26.9-Gastrointestinal tract, NOS	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	9
C23-Malignant neoplasm of gallbladder	4 (1.7)	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	Unspecified	1
		8010/3-Malignant epithelial tumor	C24.8-Overlapping lesion of biliary tract	CC (involving both intrahepatic and extrahepatic bile ducts)	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C24.9-Biliary tract, NOS	CC	1
C24.0-Malignant neoplasm of extrahepatic bile duct	1 (0.4)	8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
C24.1-Malignant neoplasm of ampulla of Vater	4 (1.7)	8000/3-Malignant tumor	C24.1-Ampulla of Vater	Unspecified	2
		8140/3-Adenocarcinoma	C24.1-Ampulla of Vater	Other ca.	2
C24.9-Malignant neoplasm of biliary tract, unspecified	6 (2.5)	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	Unspecified	3
			C24.9-Biliary tract, NOS	Unspecified	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1

**Causes of death for liver and bile duct cancer coded according to ICD codes: ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24. Abbreviations: ICD-O, International Classification of Diseases for Oncology; CC, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; NOS, not otherwise specified; Other ca., all other specific morphology codes; Unspecified, unspecified histology (no morphology information available).*

Table 4. Classification of the 240 cases identified in the 44 cohorts covered by Cancer Registry according to ICD-O and calendar period.

	Cases identified by Cancer Registry linkage (N=240)			
	<2000, n (%)	2000-2009, n (%)	2010-2019, n (%)	Total, n (%)
Classification				
ICC	0 (0.0)	2 (2.4)	7 (8.3)	9 (3.7)
ECC	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.4)
CC	0 (0.0)	0 (0.0)	4 (4.8)	4 (1.7)
HCC	24 (32.9)	29 (34.9)	30 (35.7)	83 (34.6)
Other carcinomas	11 (15.1)	6 (7.2)	8 (9.5)	25 (10.4)
Unspecified	38 (52.0)	45 (54.2)	34 (40.5)	117 (48.8)
Cirrhosis	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.4)

Abbreviations: ICD-O, International Classification of Diseases for Oncology; CC, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; Other carcinoma, all other specific morphology codes; Unspecified, unspecified histology (no morphology information available).

4. Discussion

The present study includes 47 Italian cohorts of asbestos workers and is based on the update of a larger cohort study pooling 52 cohorts of workers formerly exposed to asbestos. This exploratory study was aimed to investigate the association between occupational exposure to asbestos and risk of CC and to distinguish between HCC and ICC/ECC performing a record linkage for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registry.

Considering the causes of death identified in the 47 cohorts, we did not find an excess mortality for 'liver and intrahepatic bile duct cancer' (SMR 1.02, 95%CI 0.94-1.11 and SMR 0.98, 95%CI 0.68-1.35 for men and women, respectively). To be noted that these estimates combined causes of death mainly from HCC and ICC that reported different trends in incidence and mortality. For that purpose, a record linkage to Cancer Registries was carried out.

We identified 14 CC in the 44 cohorts covered by Cancer Registry. Most of these (12 out of 14) emerged in the last decade (2010-2019). The HCC:CC ratio in 2010-2019 was about 2.6:1, far from an expected 8:1 as reported by Mancini et al [5]. Of note, a subgroup of 21 cases with unspecified histology and with topography codes referring to bile ducts reported the same characteristics of the aforementioned cases of CC such as frequent occurrence in the last 12 years, older age (mean, 79.3±8.7 years), and long TSFE (Supplementary Table 2).

More than 60% of cases with causes of death for liver and bile duct cancer were not identified by record linkage. This result by no means can be taken as an evaluation of the quality of death certification; this was rather expected since the overlap between Cancer Registries and cohorts in the present study was far from complete, both in time and in space, as shown in Table 1. Main reasons for this were related to deaths occurred before the establishment of the registry/HDR, and to partial spatio-temporal coverage. Therefore, this preliminary experience cannot be taken as an evaluation of quality of cohort follow-up or causes of death classification. It is worth noting that the proportion of cases identified by record linkage increased with calendar period (i.e. more than 60% in the last decade) with a peak of 94% in 2015 (15 out of 16 cases were identified by Cancer Registry). To be underlined that the observed heterogeneity in Cancer Registry coverage limited the identification of cases with causes of death for liver and bile duct cancer, especially for those cases occurred more than 20 years ago. This precluded the identification of those cases of liver cancer arose from the pooled cohort study in the past and their further classification into HCC and CC.

Table 5. Cases of cholangiocarcinoma (CC) identified in the 44 cohorts covered by Cancer Registry.

Region	Company or cohort name	Industrial activity	Gender	Cause of death	ICD-O		Incidence period	Age at death	Duration of exposure (years)	TSFE (years)
				ICD code*	Morphology code	Topography code				
Piedmont	Eternit	Asbestos Cement	Female	C23-Malignant neoplasm of gallbladder	8010/3-Malignant epithelial tumor	C24.8 - Overlapping lesion of biliary tract	2010-2019	89	20	70
Veneto	OGR-Vicenza	Rolling stock maint	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2000-2009	63	16	30
	Fincantieri	Shipyard	Male	156.1-Malignant neoplasm of extrahepatic bile ducts	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2000-2009	63	7	46
	Officine Meccaniche della Stanga	Rolling stock maint and cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	76	7	60
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	65	34	45
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	67	27	39
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	89	12	44
	OGR-Vicenza	Rolling stock maint	Male	C24.0-Malignant neoplasm of extrahepatic bile duct	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	73	20	44
	Lavoratori Portuali	Harbour	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	86	24	54

(*continued*)

Region	Company or cohort name	Industrial activity	Gender	Cause of death	ICD-O		Incidence period	Age at death	Duration of exposure (years)	TSFE (years)
				ICD code*	Morphology code	Topography code				
Emilia-Romagna	Officine Gallinari	Rolling stock cons	Male	C23-Malignant neoplasm of gallbladder	8160/3-Cholangiocarcinoma	C24.9-Biliary tract, NOS	2010-2019	86	2	38
Tuscany	Breda	Rolling stock cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	64	25	43
	Breda	Rolling stock cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C24.9-Biliary tract, NOS	2010-2019	58	18	36
	Lavoratori Portuali	Harbour	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C24.0-Extrahepatic bile duct	2010-2019	76	27	53
	Cantieri Navali Apuania	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.0-Liver	2010-2019	71	22	40

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*

Abbreviations: Cons, Construction; ICD-O: International Classification of Diseases for Oncology; Maint, Maintenance; TSFE, time since first exposure.

Table 6. Causes of death for liver and bile duct cancer in the three cohorts of the province of Bologna linked to hospital discharge records (HDR)

	Cases identified by HDR linkage, N=20	HDR		
Causes of death*	**n (%)**	**ICD code**	**Primary/concomitant diagnosis**	**n**
ICD-9				
155.0-Malignant neoplasm of liver, primary	11 (55.0)	155.0-Malignant neoplasm of liver, primary	Primary	5
			Concomitant	2
		155.1-Malignant neoplasm of intrahepatic bile ducts	Primary	1
		155.2-Malignant neoplasm of liver, not specified as primary or secondary	Primary	3
155.1-Malignant neoplasm of intrahepatic bile ducts	1 (5.0)	155.2-Malignant neoplasm of liver, not specified as primary or secondary	Concomitant	1
155.2-Malignant neoplasm of liver, not specified as primary or secondary	3 (15.0)	155.0-Malignant neoplasm of liver, primary	Primary	2
			Concomitant	1
156.0-Malignant neoplasm of gallbladder	1 (5.0)	156.0-Malignant neoplasm of gallbladder	Primary	1
156.1-Malignant neoplasm of extrahepatic bile ducts	1 (5.0)	156.1-Malignant neoplasm of extrahepatic bile ducts	Primary	1
ICD-10				
C22.0-Liver cell carcinoma	3 (15.0)	155.0-Malignant neoplasm of liver, primary	Primary	2
		155.2-Malignant neoplasm of liver, not specified as primary or secondary	Primary	1

**Causes of death for liver and bile duct cancer coded according to ICD codes: ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*

For those cases identified by Cancer Registry, the vast majority (about 60%) reported cancers with unspecified histology and carcinomas other than CC or HCC. Therefore, for nearly 85% of cases, we were not able to distinguish between the two most common histological subtypes of liver cancer (i.e. HCC and CC) and this is relevant considering that these two forms differ in terms of aetiology and epidemiology [5,34].

This preliminary linkage study was aimed to identify cases of CC; however, the absolute numbers were too limited to evaluate the causal association between occupational exposure to asbestos and risk of CC. This pooled cohort study of asbestos workers has sufficient theoretical statistical power to study a rare disease like CC [35], but the overlap with Cancer Registries was too limited to evaluate all the cases notified by causes of death.

Recently, Mancini et al described the trends in liver cancer incidence in Italy using Cancer Registries data [5]. This study showed an increasing trend for ICC incidence along with a downward

and opposite trend for HCC. Moreover, the proportion of "other carcinomas and unspecified neoplasia types" out of all the cases of liver/bile duct neoplasms was 44% in men and 54% in women for 2003-2017. These figures were roughly in line with those reported in the present study. The proportion of ICC increased over the years (see Table 4). On the other hand, the proportion of HCC was stable across the three time periods. The majority of the cases identified by Cancer Registry linkage were other carcinomas/cases with unspecified histology. A global comparison of population-based cancer registry data reported that the proportion of unspecified histology cases of liver cancer ranged from the lowest levels in North America (6.2% of the total liver cases in men, 8.3% in women) to the highest levels in Southern Europe (40.5% and 48.8% in men and women, respectively) [34].

In high-income countries diagnosis of HCC and ICC through microscopic verification has decreased in favour of the use of ultrasound, computed tomography, and MRI imaging [36]. To some extent, this helps explaining the high proportion of unspecific histology cases in our study. This issue is related not only to the correct classification of ICC/ECC and HCC of "observed" cases, but also to the "expected" cases for each histological subtype. In fact, considering that only microscopically verified cases are counted for incidence and mortality estimates of histological subtypes of primary liver cancer, the burden of these diseases is widely underestimated.

To further address causality issues, other approaches should be taken into account such as case-control analysis and reevaluation of cases. For instance, cases with unspecified histology (i.e. no microscopic verification available) should be reevaluated by clinicians and pathologists based on hospital medical records along with imaging in order to differentiate the diagnosis of ICC, ECC, HCC, and other neoplasms. Clinical data, imaging together with microscopic verification should be considered to establish an accurate diagnosis.

In the framework of descriptive studies, it was suggested to reallocate the unspecific histology cases to HCC and ICC according to their relative proportion [34]. This scenario could be useful to provide more reliable incidence data; however, it would not help differentiate HCC and ICC for the purpose of causality assessment.

Some methodological considerations need to be addressed in addition to those relating to record linkage, already mentioned above. There is high variability in data quality for liver cancer from population-based cancer registries; high variability was shown also by coding of CC [37]. Changes in ICD-O classification over time have resulted in some misclassification of ICC and ECC. For instance, in 2000 the ICD-O-3 allows Klatskin tumours to be cross-referenced to either ICC (C22.1) or ECC (C24.0) [30]. Misclassification might also have occurred considering that it is not recommended to perform a biopsy in case of adverse clinical conditions of the patient, while the ENCR recommendations dissuaded to use specific morphological codes without microscopic confirmation [31].

Italy as well as other countries with high socio-demographic index have been characterised by unfavourable trend of liver cancer driven by unidentified factors other than HBV, HCV, and alcohol consumption [38]. These along with differences in terms of aetiology and epidemiology of HCC, ICC and ECC should be taken into account for future investigations considering the potential role of asbestos exposure as well.

A variety of non-occupational risk factors contributed to the onset of CC [9]. No data on personal habits and medical conditions of the subjects included in the pooled cohort study were available. Alcohol drinking, smoking habits, and other liver diseases might play a role in the development of CC. These confounders are more common among subjects with low socio-economic status [39-41] like workers formerly exposed to asbestos. This might overestimate the risk of CC in our cohort. However, in a recent case-control study on CC and asbestos, Brandi et al reported slightly higher estimates (adjusted for smoking status and socioeconomic class) than those reported in the univariate analysis [15].

Occupational risk factors other than asbestos might be considered as well. IARC classified 1,2-dichloropropane and dichloromethane in Group 1 (carcinogenic to humans) and 2A (probably

carcinogenic to humans), respectively [42]. However, these solvents were not commonly used in the industrial sectors included in the present study. Nevertheless, it is within the bounds of possibility that these chemical substances, or other substances whose carcinogenicity is not yet known, could have contributed to the development of CC.

5. Conclusions

Present data show feasibility along with limits of using record linkage of mortality records with Cancer Registry records to identify cases of CC and to further classify them into ICC or ECC forms. The real burden of ICC and ECC related to occupational exposure to asbestos needs to be further investigated. The high proportion of unspecific histology cases hampered to firmly support the hypothesis of a causal association between occupational exposure to asbestos and the risk of CC.

Further studies are needed to explore the association between occupational exposure to asbestos and CC, including multicentre case-control studies with microscopically verified cases of ICC and ECC along with estimates of occupational and non-occupational exposure to asbestos. The identification of ICC/ECC and HCC among unspecific histology cases is of paramount importance to better understanding the epidemiology of these diseases and establish more effective and targeted liver cancer screening strategies.

Supplementary Materials: Supplementary Table 1, Supplementary Table 2.

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Informed Consent Statement: The processing of the data is carried out in compliance with data protection laws for statistical and scientific purposes and only with operations strictly essential for conducting the study.

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Declaration On The Use Of Ai: none

References

1. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016 May;13(5):261-280.
2. Cardinale V, Semeraro R, Torrice A, et al. Intrahepatic and extrahepatic cholangiocarcinoma: New insight into epidemiology and risk factors. World J Gastrointest Oncol. 2010 Nov 15;2(11):407-416.
3. Hemminki K, Försti A, Hemminki O, et al. Long-term incidence and survival trends in cancer of the gallbladder and extrahepatic bile ducts in Denmark, Finland, Norway and Sweden with etiological implications related to Thorotrast. Int J Cancer. 2022 Jul 15;151(2):200-208.
4. Bergquist A, von Seth E. Epidemiology of cholangiocarcinoma. Best Pract Res Clin Gastroenterol. 2015 Apr;29(2):221-232.
5. Mancini S, Bucchi L, Zamagni F, et al. Trends in Liver Cancer Incidence and Survival in Italy by Histologic Type, 2003-2017. Cancers (Basel). 2022 Dec 14;14(24):6162.
6. Florio AA, Ferlay J, Znaor A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. Cancer. 2020 Jun 1;126(11):2666-2678.
7. Alvaro D, Crocetti E, Ferretti S, et al. Descriptive epidemiology of cholangiocarcinoma in Italy. Dig Liver Dis. 2010 Jul;42(7):490-495.
8. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol. 2019 Jul;71(1):104-114.
9. Brandi G, Tavolari S. Asbestos and Intrahepatic Cholangiocarcinoma. Cells. 2020 Feb 12;9(2):421.

10. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int. 2019 May;39 Suppl 1:19-31.
11. Kumagai S, Kurumatani N, Arimoto A, Ichihara G. Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med. 2013 Jul;70(7):508-510.
12. Kumagai S, Sobue T, Makiuchi T, et al. Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers. Occup Environ Med. 2016 Aug;73(8):545-552.
13. Vlaanderen J, Straif K, Martinsen JI, et al. Cholangiocarcinoma among workers in the printing industry: using the NOCCA database to elucidate the generalisability of a cluster report from Japan. Occup Environ Med. 2013 Dec;70(12):828-830.
14. Brandi G, Straif K, Mandrioli D, et al. Exposure to Asbestos and Increased Intrahepatic Cholangiocarcinoma Risk: Growing Evidences of a Putative Causal Link. Ann Glob Health. 2022 Jun 13;88(1):41.
15. Brandi G, Di Girolamo S, Farioli A, et al. d Asbestos: a hidden player behind the cholangiocarcinoma increase? Findings from a case-control analysis. Cancer Causes Control. 2013 May;24(5):911-918.
16. Farioli A, Straif K, Brandi G, et al. Occupational exposure to asbestos and risk of cholangiocarcinoma: a population-based case-control study in four Nordic countries. Occup Environ Med. 2018 Mar;75(3):191-198.
17. Vasuri F, Deserti M, Corradini AG, et al. Asbestos exposure as an additional risk factor for small duct intrahepatic cholangiocarcinoma: a pilot study. Sci Rep. 2023 Feb 13;13(1):2580.
18. Grosso F, Croce A, Libener R, et al. Asbestos fiber identification in liver from cholangiocarcinoma patients living in an asbestos polluted area: a preliminary study. Tumori. 2019 Oct;105(5):404-410.
19. Cook PM. Review of published studies on gut penetration by ingested asbestos fibers. Environ Health Perspect. 1983 Nov;53:121-30.
20. Brandi G, Tavolari S. Asbestos and Intrahepatic Cholangiocarcinoma. Cells. 2020 Feb 12;9(2):421.
21. Theise ND, Saxena R, Portmann BC, et al. The canals of Hering and hepatic stem cells in humans. Hepatology. 1999 Dec;30(6):1425-33.
22. Grosso F, Randi L, Croce A, et al. Asbestos fibers in the gallbladder of patients affected by benign biliary tract diseases. Eur J Gastroenterol Hepatol. 2015 Jul;27(7):860-4.
23. Ferrante D, Angelini A, Barbiero F, et al. Cause specific mortality in an Italian pool of asbestos workers cohorts. Am J Ind Med. 2024 Jan;67(1):31-43.
24. Ferrante D, Chellini E, Merler E, et al. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. Occup Environ Med. 2017 Dec;74(12):887-898.
25. Magnani C, Silvestri S, Angelini A, et al. Italian pool of asbestos workers cohorts: asbestos related mortality by industrial sector and cumulative exposure. Ann Ist Super Sanita. 2020 Jul-Sep;56(3):292-302.
26. Luberto F, Ferrante D, Silvestri S, et al. Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy. Environ Health. 2019 Aug 7;18(1):71.
27. Girardi P, Merler E, Ferrante D, et al. Factors Affecting Asbestosis Mortality Among Asbestos-Cement Workers in Italy. Ann Work Expo Health. 2020 Jul 1;64(6):622-635.
28. Barone-Adesi F, Ferrante D, Chellini E, et al. Role of asbestos clearance in explaining long-term risk of pleural and peritoneal cancer: a pooled analysis of cohort studies. Occup Environ Med. 2019 Sep;76(9):611-616.
29. Azzolina D, Consonni D, Ferrante D, et al. Rate advancement measurement for lung cancer and pleural mesothelioma in asbestos-exposed workers. Thorax. 2023 Aug;78(8):808-815.
30. World Health Organization. International Classification of Diseases for Oncology (ICD-O), 3rd ed., 1st revision. World Health Organization, 2013.
31. Tyczynski JE, Démaret E, Parkin DM. Standards and Guidelines for Cancer Registration in Europe. The ENCR Recommendations, IARC Technical Publication No. 40; International Agency for Research on Cancer: Lyon, France, 2003.
32. Breslow NE, Day NE. Statistical methods in cancer research (Volume II): The design and analysis of cohort studies. IARC Scientific Publication No. 82. Lyon, 1987:1-406.
33. Marsh GM, Youk AO, Stone RA, et al. OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. J Occup Environ Med. 1998 Apr;40(4):351-362.
34. Rumgay H, Ferlay J, de Martel C, et al. Global, regional and national burden of primary liver cancer by subtype. Eur J Cancer. 2022 Jan;161:108-118.
35. Armstrong B. A simple estimator of minimum detectable relative risk, sample size, or power in cohort studies. Am J Epidemiol. 1987 Aug;126(2):356-358.
36. Rutherford MJ, Arnold M, Bardot A, et al. Comparison of liver cancer incidence and survival by subtypes across seven high-income countries. Int J Cancer. 2021 Dec 15;149(12):2020-2031.
37. Bannon F, Di Carlo V, Harewood R, et al. Survival trends for primary liver cancer, 1995–2009: analysis of individual data for 578,740 patients from 187 population-based registries in 36 countries (CONCORD-2). Ann Cancer Epidemiol. 2019;3:6.
38. Liu Z, Jiang Y, Yuan H, et al. The trends in incidence of primary liver cancer caused by specific etiologies:

Results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. J Hepatol. 2019 Apr;70(4):674-683.
39. Askgaard G, Fleming KM, Crooks C, et al. Socioeconomic inequalities in the incidence of alcohol-related liver disease: A nationwide Danish study. Lancet Reg Health Eur. 2021 Jul 13;8:100172.
40. Casetta B, Videla AJ, Bardach A, et al. Association Between Cigarette Smoking Prevalence and Income Level: A Systematic Review and Meta-Analysis. Nicotine Tob Res. 2017 Nov 7;19(12):1401-1407.
41. Wang Y, Kong L, Ye C, et al. Causal impacts of educational attainment on chronic liver diseases and the mediating pathways: Mendelian randomization study. Liver Int. 2023 Nov;43(11):2379-2392.
42. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Some Chemicals Used as Solvents and in Polymer Manufacture. Lyon, France: IARC, 2017.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. References related to cohorts included in the study.

Company or cohort name	References
Miners [1,2]	[1] Silvestri S, Ferrante D, Giovannini A, et al. Asbestos Exposure of Chrysotile Miners and Millers in Balangero, Italy. *Ann Work Expo Health*. 2020 Jul 1;64(6):636-644. [2] Ferrante D, Mirabelli D, Silvestri S, et al. Mortality and mesothelioma incidence among chrysotile asbestos miners in Balangero, Italy: A cohort study. *Am J Ind Med.* 2020 Feb;63(2):135-145.
Eternit [3]	[3] Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med.* 2008 Mar;65(3):164-170.
SACA [4]	[4] Ferrante D, Bertolotti M, Todesco A, et al. Mortality among asbestos cement workers:the cohort of the S.A.C.A. plant in Cavagnolo (Italy). *Biomedical Statistics and Cancer Epidemiology* 2008; 2:171-177.
Wives of Eternit workers [5]	[5] Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect* 2007;115:1401-5.
Fibronit [6]	[6] Oddone E, Ferrante D, Cena T, et al. [Asbestos cement factory in Broni (Pavia, Italy): a mortality study]. *Med Lav* 2014;105:15-29.
Cantieri Navali Genova [7]	[7] Merlo DF, Bruzzone M, Bruzzi P, et al. Mortality among workers exposed to asbestos at the shipyard of Genoa, Italy: a 55 years follow-up. *Environ Health*. 2018 Dec 29;17(1):94.
Edilit [8]	[8] Fedeli U, Fadda P, Paruzzolo P, et al. Studio prospettico di mortalità per tumori in una coorte di esposti a cemento asbesto. *G Ital Med Lav Erg* 2004, 26 (4 Suppl):227.
Officine di Cittadella [9,10]	[9] Simonato L, Tessari R, Canova C. [Controversy unsupported by data]. *Med Lav.* 2004;95:412-413. [10] Tessari R, Canova C, Simonato L. [Epidemiological investigation on the health status of employees in two factories manufacturing and repairing railway rolling stock: a historical perspective study of mortality]. *Med Lav* 2004;95:381-391.
Officine Meccaniche della Stanga [9,10]	[9] Simonato L, Tessari R, Canova C. [Controversy unsupported by data]. *Med Lav.* 2004;95:412-413. [10] Tessari R, Canova C, Simonato L. [Epidemiological investigation on the health status of employees in two factories manufacturing and repairing railway rolling stock: a historical perspective study of mortality]. *Med Lav* 2004;95:381-391.
Artclit, Cemental, Cemiant, Fibrotubi, ICAR Eternit, Itamiant, Sidercam, Uprocem, Maranit, Superlit [11]	[11] Luberto F, Amendola P, Belli S, et al. Studio di mortalità degli addetti alla produzione di manufatti in cemento amianto in Emilia-Romagna [Mortality study of asbestos cement workers in Emilia-Romagna]. *Epidemiol Prev.* 2004 Jul-Oct;28(4-5):239-246.
Casaralta [12]	[12] Pavone VL, Scarnato C, Marinilli P, et al. Mortalità in una coorte di addetti alla costruzione e riparazione di carrozze ferroviarie in un'azienda di Bologna [Mortality in a cohort of railway Rolling stockuction and repair workers in Bologna]. *Med Lav.* 2012 Mar-Apr;103(2):112-122.
Derbit [13]	[13] Zanardi F, Salvarani R, Cooke RM, et al. Carcinoma of the pharynx and tonsils in an occupational cohort of asphalt workers. *Epidemiology*. 2013;24(1):100-3.
Breda [14]	[14] Gasparrini A, Pizzo AM, Gorini G, et al. Prediction of mesothelioma and lung cancer in a cohort of asbestos exposed workers. *Eur J Epidemiol*. 2008;23(8):541-546.

Company or cohort name	References
Fibronit [15]	[15] Raffaelli I, Festa G, Seniori Costantini A, et al. Studio sulla mortalità degli addetti alla produzione in un'azienda di manufatti in cemento amianto a Carrara, Italia. *Med Lav* 2007; 98: 156-163.
Santa Lucia [16]	[16] Fedi A, Blagini B, Melosi A, et al. Ricostruzione dell'esposizione, studio di mortalità della coorte di lavoratori e intervento sugli ex-esposti ad amianto di una azienda metalmeccanica [Assessment of asbestos exposure, mortality study, and health intervention in workers formerly exposed to asbestos in a small factory making drying machines for textile finishing and the paper mill industry in Pistoia, Italy]. *Med Lav.* 2005 May-Jun;96(3):243-249.
Sacelit [17,18]	[17] Fazzo L, Cernigliaro A, De Santis M, et al. Occupational cohort study of asbestos-cement workers in a contaminated site in Sicily (Italy). *Epidemiol Prev.* 2020 Mar-Jun;44(2-3):137-144. [18] Fazzo L, Nicita C, Cernigliaro A, et al. Mortalità per cause asbesto-correlate e incidenza del mesotelioma fra i lavoratori del cemento-amianto di San Filippo del Mela (Messina) [Mortality from asbestos-related causes and incidence of pleural mesothelioma among former asbestos cement workers in San Filippo del Mela (Sicily)]. *Epidemiol Prev*. 2010 May-Jun;34(3):87-92.
Australian Blue asbestos [19]	[19] Merler E, Ercolanelli M, de Klerk N. [Identification and mortality of Italian emigrants returning to Italy after having worked in the crocidolite mines at Wittenoon Gorge, Western Australia]. *Epidemiol Prev* 2000;24:255-256.

Supplementary Table 2. Cancers with unspecified histology and topography codes referring to bile ducts identified in the 44 cohorts covered by Cancer Registry.

				Cause of death	ICD-O					
Region	**Company or cohort name**	**Industrial activity**	**Gender**	**ICD code***	**Morphology code**	**Topography code**	**Incidence period**	**Age at death**	**Duration of exposure (years)**	**TSFE (years)**
Piedmont	Amiantifera di Balangero	Chrysotile Mine	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	93	28	67
	Eternit	Asbestos Cement	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2010-2019	79	26	54
	Eternit	Asbestos Cement	Male	C23-Malignant neoplasm of gallbladder	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	73	3	44
	SACA	Asbestos Cement	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	82	0.33	57
Liguria	Cantieri Navali Genova	Shipyards	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	83	17	44
	Cantieri Navali Genova	Shipyards	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	1990-1999	65	17	27
	Cantieri Navali Genova	Shipyards	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	87	27	72
Veneto	Officine Grandi Riparazioni FS	Rolling stock maint	Male	155-Malignant neoplasm of liver and intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	1990-1999	77	37	55
	Compagnia lavoratori Portuali	Harbour	Male	155.0-Malignant neoplasm of liver, primary	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	77	35	54
	Officine Grandi Riparazioni FS	Rolling stock maint	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	58	2	35

	Fincantieri	Shipyard	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	84	5	45
	Fincantieri	Shipyard	Male	156.1-Malignant neoplasm of extrahepatic bile ducts	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	77	25	51
	Fincantieri	Shipyard	Male	156.2-Malignant neoplasm of ampulla of Vater	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2000-2009	88	1	47
	Fincantieri	Shipyard	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	85	3	50
Emilia-Romagna	ICAR Eternit	Asbestos Cement	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	79	19	36
	Cemental/ ICAR Eternit	Asbestos Cement	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	71	2	43
Tuscany	Cantieri Navali Apuania	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	81	3	34
	Compagnia lavoratori Portuali	Harbour	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	87	26	52
	Borma	Glassworks	Female	C22.9-Malignant neoplasm of liver, not specified as primary or secondary	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2010-2019	93	5	74
	Borma	Glassworks	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	76	22	43
	Fervet	Rolling stock maint and cons	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	71	0.01	49

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*
Abbreviations: Cons, Construction; ICD-O, International Classification of Diseases for Oncology; Maint, Maintenance; TSFE, time since first exposure.