Volume 114 5/2023

Rivista fondata nel 1901 da Luigi Devoto Issn 0025 - 7818

La Medicina del Lavoro

Organo della Società Italiana di Medicina del Lavoro

Work, Environment & Health

Official Journal of the Italian Society of Occupational Medicine

www.lamedicinadellavoro.it

Editorial

Reviews, Commentaries, Perspectives

Original Articles

Case Report

Poste Italiane s.p.a. - Sped. in A. P. - D.L. 353/2003 (conv. in L. 27/02/2004 n. 46) art. 1, comma 1, DCB parma - Finito di stampare nel mese di Ottobre 2023

Mattioli 1885

Volume 114

Issn 0025-7818

Rivista fondata nel 1901 da Luigi Devoto

eIssn 2532-1080

La Medicina del Lavoro

Organo della Società Italiana di Medicina del Lavoro

Work, Environment & Health

Official Journal of the Italian Society of Occupational Medicine

Editorial office
La Medicina del Lavoro
Clinica del Lavoro «L. Devoto»
Via San Barnaba, 8 - 20122 Milano (Italy)
Tel. 02/50320125 - Fax 02/50320103
http://www.lamedicinadellavoro.it
redazione@lamedicinadellavoro.it

Publisher
Mattioli 1885 srl - Casa Editrice
Strada di Lodesana 649/sx, Loc. Vaio - 43036 Fidenza (PR)
Tel. 0524/530383 - Fax 0524/82537
e-mail: edit@mattioli1885.com
www.mattioli1885.com

Pubblicazione bimestrale - Direttore Responsabile: Antonio Mutti
Autorizzazione del Presidente del Tribunale di Milano 10/5/1948 Reg. al N. 47

La Medicina del Lavoro è indicizzata da / La Medicina del Lavoro is indexed in:
PubMed/Medline; Embase/Excerpta Medica; Abstracts on Hygiene; Industrial Hygiene Digest; Securité et Santé au Travail Bit-CIS; Sociedad Iberoamericana de Informaciòn Cientifica (SIIC); Science Citation Index Expanded (SciSearch®); Journal Citation Report/Science Edition; ISI Web of Science; Scopus (Elsevier); Bibliovigilance

La Medicina del Lavoro

Editorial

Med. Lav. 2023; 114 (5): e2023045
DOI: 10.23749/mdl.v114i5.15260

The Evolving Work Landscape and the Intersection of Technics, Technology, and Occupational Health*

Work is historically and clearly inscribed in the DNA of Occupational Medicine. It has been so since its founder Bernardino Ramazzini wrote at the beginning of the 18th century, *"…nor did I disdain visiting the basest workshops and workshops to observe all the means used in the mechanical arts carefully…"*, and later talking about workplaces and the observation of people at work "*they are in this sense the only school in which one can be educated and describe what is most interesting and above all provide means of healing and prevention of diseases that attack the creators…*" [1].

It has been so since the beginning of the 20th century, when Luigi Devoto, father of modern Italian Occupational Medicine, fought for the structure to study and treat occupational diseases called the "*Clinica del Lavoro*". He had a dialectical confrontation with another illustrious clinician, Gaetano Pini, who argued that the "Workers' Clinic" denomination would be more appropriate to unequivocally identify the purposes of a structure finalized to benefit the working class. Devoto's famous argument to support his position was "*…because it is work that is sick, and it is this that must be treated so that workers' diseases can be prevented*". He had an opportunity to further clarify his thoughts in a conference held in Brescia in 1906, where he stated, "*It is necessary to purify work from its thorns and stains. The enlightening help of work physiology and pathology is indispensable, so we must have faith in science*". [2]

Therefore, working technical and human contents and knowledge and pathophysiological knowledge of medical discipline based on scientific evidence (today, scientific evidence-based medicine) became indispensable supports for reducing and eliminating work-related risks. However, Devoto had already demonstrated constant awareness that we had to start from work in 1901 by heading the first Occupational Medicine journal in the world that he was about to found, *'Il Lavoro'* (in English, "The Work") [3] which then became *'La Medicina del Lavoro'* (in English, "Work's Medicine") [4] after about twenty years. This concept also led to the English subheading 'Work, Environment & Health' chosen a few years ago for the journal's current edition. [5]

Certainly, in Ramazzini's time, the work's technical components were based on notions and norms empirically acquired or handed down by tradition and, to a lesser extent, on the application of scientific knowledge transmitted from father to son, family members, or in a broader context or among members of their workshop. On the contrary, the technics that Devoto dealt with were born during the 1st and 2nd industrial revolutions, configured as a wealth of knowledge, increasingly specialized, subject to continuous innovation, and requiring specific studies and the associated training provided in various professional polytechnic schools and universities.

It is with the technics, and particularly those of the 3rd and 4th industrial revolutions that have gradually characterized work from the 19th century to today, that Occupational Medicine has been called to deal with, has grown and evolved, having to keep up with the evolution of raw and secondary materials, the manufacturing technics of their instruments, the working environments (from lighting

*This editorial is based on the introductory lecture delivered at the first session of the 85 th National Congress on Occupational Medicine (Turin, 20-22 September 2023) technology to the microclimate) the physical and mental workload, the availability of individual and collective means of prevention and protection.

The traditional risks to the health and safety of workers have been greatly reduced, some even disappeared, at least in the most advanced production realities, by the radical technical innovations introduced; we must be aware of this, above all, to guarantee, increase, and often revolutionize, productivity and profitability of manual and intellectual work. However, we must remember that also Occupational Medicine contributed to reducing occupational risks and improving working conditions by demonstrating historical pathologies of work, from silicosis to intoxications caused by metallic elements or volatile chemical compounds, and through the increasingly in-depth understanding of the pathogenetic mechanisms of work-related diseases.

The objective was, therefore, to shift to the problems relating to new production methods and work organization. The osmosis between polytechnic and medical-biological disciplines became the condition for being able to foster research to achieve the compatibility between work and man on one side and between man and work on the other, mainly in the prevention of risks associated with the introduction of new materials, with multiple and low exposures to toxic substances (sometimes comparable with those brought by polluted general environments) or to musculoskeletal and psychosocial risk factors. The focus is shifting to a more demanding objective: achieving an increasingly widespread psychophysical well-being of men at work.

To realize or at least get close to objectives of this nature, further developments are necessary in the relationships between our two worlds, with interaction and integration at a higher level, shifting our reflections to scientific and theoretical insights into technology applications. And this seems to me to be the most suitable place to do it, given that, among other things, the diffusion of term technology is credited to a doctor, scientist, and professor at Harvard, Jacob Bighelow, author of the treatise "Elements of Technology" in 1829 [6], in which he broadened his horizons to mechanics and the non-biological sciences.

According to Bighelow, technology meant synthetically "systematic treatment of an art", but the technology most appropriate and comprehensive of the problems that we are called to face at the beginning of the 21st century is that based on theoretical formulations, derived by deduction from previous knowledge, verified and validated through experiments. However, we cannot deny that there is still room for further discoveries based on observation. It is at this level that, in my opinion, the interaction between our disciplines is already taking shape in the design, decision, and implementation of the production processes so that the results desired by technologists are obtained first and foremost, but at the same time, ensuring that prevention is considered from the design phase, so that unwanted effects are reduced to a minimum, in our case the negative effects on the psychophysical health of workers and in a broader sense on environmental and living conditions.

An example, on the technological side, of these concepts was that of William Vanderburg [7], known as "preventive engineering" and well exemplified by the metaphor of driving a car by focusing on its performance as indicated by the instruments on the dashboard, and only occasionally looking outside to see where it is going. That represents a reality where engineers, managers, and regulators make decisions without or with little regard for the consequences that are mostly outside their domains of competence, from where they cannot "see" them.

This has meant that conventional approaches have been fundamentally non-preventive and non-precautionary in structure, characterized by the production of gross wealth without considering social and environmental costs from the outset and without verifying the correlation between wealth creation and human and environmental well-being.

A collaboration and disciplinary integration between technologists and occupational physicians in the methodological approaches of the design phases and the decision-making process would create the ideal conditions for obtaining the desired net results, also allowing us not to have to intervene *post hoc* in attempting to remedy conditions of risk created in the application of the new technics, with higher costs for remedial interventions and above all with the addition of certainly predictable human costs.

Furthermore the current technology must face and respond to challenges posed by the 4th Industrial Revolution, which is questioning those that, from Fordism onwards, were considered cornerstones of work, such as its times and places, hierarchies, and organizational methods. Technology which, therefore, tends to move away from its merely mechanistic sphere to place itself in an increasingly open and engaging position with other and new knowledge, approaching contents such as those underlying the definition that gives the Encyclopedia Britannica: "*the application of scientific knowledge to the practical aims of human life or to the change and manipulation of the human environment*" [8].

Finally, I would like to recall a crucial point for me: that of the training curricula of future technologists and doctors, whose shortcomings, as Vanderburgh himself noted, are then laboriously attempted to be remedied, with higher costs and sometimes unsatisfactory results, in the following phase of professional practice [7]. It is a matter of guaranteeing in degree courses and specialization schools reciprocal, possibly integrated teaching paths of the main contents that join our disciplinary areas.

Pietro Apostoli
Honorary Professor of Occupational Medicine
at the University of Brescia

References

1. Ramazzini B, De Morbis Artificum Diatriba. 1700, Capponi Publ, Modena.
2. Busacchi V, D'Antuono G, *La Medicina del Lavoro nei suoi sviluppi storici*, Arti grafiche - Linotypia E. Cossidente, Roma 1967, p. 105.
3. Il Lavoro. 1901 https://collezioni.unimi.it/dcb/rivlavoro/index.php
4. La Medicina del Lavoro. 1925 https://collezioni.unimi.it/dcb/rivlavoro/index.php
5. Mutti A. Cultural background and methods of Occupational Medicine are increasingly used to characterize environmental pollution and its health effects. *Med Lav*. 2020;111(1):6-9. https://mattioli1885journals.com/index.php/lamedicinadellavoro/article/view/9190
6. Bigelow, Jacob, 1786-1879. Elements of technology, taken chiefly from a course of lectures delivered at Cambridge, on the application of the sciences to the useful arts. Retrieved from the Digital Public Library of America, http://catalog.hathitrust.org/Record/001510374. (Last Accessed September 27, 2023.)
7. Vanderburg W. Preventive Engineering: Strategy for Dealing with Negative Social and Environmental Implications of Technology. *J Prof Iss Eng Ed Pr*. Vol. 121, No. 3, July 1995.
8. Encyclopedia Britannica, Technology, last updated August 2023 https://www.britannica.com

La Medicina del Lavoro

Reviews, commentaries, perspectives

Med Lav 2023; 114 (5): e2023040
DOI: 10.23749/mdl.v114i5.15065

Per- and Poly-fluoroalkyl Substances (PFAS) Exposure and Risk of Kidney, Liver, and Testicular Cancers: A Systematic Review and Meta-Analysis

Monireh Sadat Seyyedsalehi[1,2], Paolo Boffetta[1,3,4,*]

[1]School of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[2]Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA
[4]Department of Family, Population and Preventive Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA

Keywords: Kidney; Occupational Factors; Liver; Testis; Malignant; Water; Perfluorooctanoic Acid; PFAS; Perfluorooctane Sulfonic Acid

Abstract

Introduction: *Per- and poly-fluoroalkyl substances (PFASs) are a large, complex group of synthetic chemicals humans can be exposed to from occupational or environmental sources. In this systematic review and meta-analysis, we examined the association between PFAS exposure, particularly Perfluorooctanoic Acid (PFOA), and Perfluorooctane Sulfonic Acid (PFOS), and risk of kidney, liver, and testicular cancer.* **Methods:** *We systematically searched PubMed to identify cohort and case-control studies reported after the Monograph of the International Agency for Research on Cancer and the Toxicological Profile of the Agency for Toxic Substances and Disease Registry. We assessed the quality of the studies by using a modified version of the Newcastle-Ottawa Scale (NOS). Forest relative risk (RR) plots were constructed for liver, kidney, and testicular cancer. We conducted stratified analyses by geographic region, study design, quality score, outcome, years of publication, exposure source, and PFAS type. A random-effects model was used to address heterogeneity between studies.* **Results:** *Fifteen studies, including ten cohort studies, three case-control studies nested in a cohort, and two case-control studies were included after removing duplicate and irrelevant reports. We found an association between overall PFAS exposure and the risk of kidney cancers (RR=1.18, 95% CI =1.05-1.32; I =52.8%, 11 studies). Also, we showed an association between high-level exposure to PFAS and kidney cancer (RR=1.74, 95% CI =1.23-2.47; p=0.005) and testicular cancer (RR=2.22, 95% CI =1.12-4.39; p=0.057). There was no association with liver cancer. We found no heterogeneity by geographical region, PFAS type, study design, outcome, quality score, year of publication, or exposure source. Only two studies reported results among women.* **Conclusions:** *We detected an association between overall PFAS exposure and kidney cancer and high doses of PFAS with testicular cancer. However, bias and confounding cannot be excluded, precluding a conclusion in terms of causality.*

Abbrevations:

- Agency for Toxic Substances and Disease Registry; ATSDR
- International Agency for Research on Cancer; IARC
- inflammatory bowel disease; IBD
- Hepatocellolar carcinoma; HCC
- Nitrogen dioxide; NO2
- Odds ratio; OR
- Risk ratio, rate ratio;R R
- Standardized mortality ratio;SMR

- Standardized incidence ratio; SIR
- Perfluorooctanoic Acid; PFOA
- Per- and poly-fluoroalkylsubstances; PFAS
- Perfluorooctane sulfonic acid; PFOS

1. Introduction

Per- and poly-fluoroalkyl substances (PFASs) are a large, complex group of synthetic chemicals that are thermally and chemically stable in the environment [1]. Since the 1940s, these agents have been used in various industries, such as aerospace, automotive, construction, and electronics. Also, they are used to produce stain- and water-resistant fire-fighting foams, cleaning products, and paints [2].

PFAS may be released into water, air, and soil. Hence humans can be exposed to these substances through occupational or environmental sources [3, 4]. Chemically, there are several types of PFAS. However, the most common types are perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexanesulfonic acid (PFHxS) [1].

Previous studies reported that exposure to some PFAS types may be associated with health effects [5, 6]. Cancer incidence is one of the most pressing concerns concerning PFAS exposure [7]. The International Agency for Research on Cancer (IARC) 2017 classified PFOA as a possible human carcinogen based on limited epidemiologic evidence for kidney and testicular cancer [8]. In addition, previous epidemiological and animal studies reported some association between these substances and other cancer varieties, such as liver cancer [9, 10]. Worldwide, 431,288, 905,677, and 74,458 people can be diagnosed yearly with kidney, liver, and testicular cancer [11].

To better clarify the possible effects of PFAS on cancer incidence and mortality, we conducted a systematic review and meta-analysis to examine the association between occupational and environmental exposure to PFA, emphasizing PFOS and PFOA, and the risk of kidney, liver, and testicular cancer.

2. Methods

2.1. Data Sources, Search Strategy, Selection Criteria, and Quality Assessment

First, we searched the reference lists of the IARC Monograph on PFOA [8] and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for perfluoroalkyls [12]. And then, searches were undertaken on July 8, 2023, for peer-reviewed publications in PubMed with no limit according to year of publication and language to identify more recent studies. We included studies on incidence or mortality from kidney, liver, and testicular cancers and exposure to PFAS, including PFOA and PFOS.

The search strategy was designed using MeSH terms ("PFOA"[Text Word] OR "PFOS"[Text Word] OR "PFAS"[Text Word]) AND ("kidney"[Text Word] OR "liver"[Text Word] OR "testicular"[Text Word] OR "testis"[Text Word] OR "Hepatocellular"[Text Word]) AND ("cancer"[Text Word]). We included cohort, case-control, and ecological studies of occupational and environmental exposure to PFAS, including studies based on serum levels of PFAS. Studies involving animals were excluded.

Two reviewers (MSS and PB) independently reviewed the list of titles and abstracts, and the final selection was based on the full text of potentially relevant articles. If multiple reports were based on the same database, we included only the most informative article, typically based on the most recent update. The meta-analysis was performed according to the STROBE statement [13] and reported according to the PRISMA statement (Supplementary Table 1) [14].

The data extraction file contained demographic characteristics of the original studies, including author name, year of publication, country, type of study (case-control, cohort, ecologic), patient characteristics (sex, ethnicity), type of cancer, type of PFAS, exposure source (occupational or environmental),

Received 01.08.2023 - Accepted 10.08.2023
*Corresponding Author: Paolo Boffetta, University of Bologna; E-mail: paolo.boffetta@unibo.it

Table 1. Results of the metanalyses stratified by region, outcome, study design, year of publication, gender, and quality score.

Characteristic	N risk estimates	RR, 95% CI	p heterogeneity
	Kidney cancer		
Region			
North America	7	1.25(1.04-1.50)	
Europe	3	1.08(0.90-1.31)	0.49
Others	1	1.27(0.96-1.68)	
Study design			
Cohort	8	1.12(0.99-1.26)	
Nested case control	2	1.52(1.22-1.89)	0.04
Case control	1	1.10(0.88-1.37)	
Quality score			
Low quality (<8)	7	1.14(1.00-1.30)	0.60
High quality (>=8)	4	1.24(0.93-1.65)	
Outcome			
Incidence	9	1.16(1.04-1.29)	0.98
Mortality	3	1.15(0.60-2.20)	
Year of publication			
<2014	4	1.12(1.01-1.24)	0.54
>=2014	7	1.19(1.00-1.42)	
Exposure			
Occupational	3	1.15(0.60-2.20)	0.96
Environmental	8	1.17(1.05-1.31)	
PFAS type			
PFOA	6	1.23(0.99-1.51)	
PFOS	1	1.39(1.04-1.86)	0.41
PFAS	4	1.12(0.95-1.31)	
Dose category			
Low	7	0.98(0.83-1.17)	
Medium	8	1.38 (1.09-1.74)	0.03*
High	7	1.74 (1.23-2.47)	
	Liver cancer		
Region			
North America	8	1.08(0.83-1.42)	
Europe	5	0.97(0.83-1.13)	0.63
Others	3	1.20(0.72-2.01)	
Study design			
Cohort	10	0.94(0.83-1.08)	
Nested case control	3	1.37(0.65-2.87)	0.25
Case control	3	1.31(0.85-2.00)	

Table 1 (*Continued*)

Characteristic	N risk estimates	RR, 95% CI	p heterogeneity
Quality score			
Low quality (<8)	10	1.02(0.90-1.14)	0.55
High quality (>=8)	6	1.16(0.77-1.74)	
Outcome			
Incidence	13	1.03(0.90-1.18)	0.23
Mortality	5	1.31(0.90-1.90)	
Year of publication			
<2014	6	0.96(0.80-1.16)	0.43
>=2014	10	1.06(0.91-1.24)	
Exposure			
Occupational	5	1.31(0.90-1.90)	0.18
Environmental	11	1.00(0.88-1.13)	
PFAS type			
PFOA	8	1.05(0.93-1.18)	
PFOS	4	1.86(0.81- 4.25)	0.07
PFAS	4	0.91(0.82-1.02)	
Dose category			
Low	8	1.12 (0.85-1.48)	
Medium	4	1.22 (0.66-2.25)	0.37*
High	9	1.01 (0.68-1.50)	
	Testicular cancer		
Region			
North America	5	1.28(0.99-1.64)	
Europe	2	1.19(0.65-2.17)	0.33
Others	1	0.76(0.40-1.44)	
Study design			
Cohort	7	1.14(0.94-1.37)	
Nested case control	0	-	0.67
Case control	1	1.00(0.58-1.73)	
Quality score			
Low quality (<8)	6	1.00(0.79-1.26)	0.11
High quality (>=8)	2	1.35(1.01-1.80)	
Outcome			
Incidence	5	1.10(0.88-1.39)	0.44
Mortality	3	1.80(0.53-6.14)	
Year of publication			
<2014	5	1.28(0.99-1.64)	0.30
>=2014	3	1.01(0.69-1.46)	

Characteristic	N risk estimates	RR, 95% CI	p heterogeneity
Exposure			
Occupational	3	1.80(0.53-6.14)	0.44
Environmental	5	1.10(0.88-1.39)	
PFAS type			
PFOA	5	1.28(0.99-1.64)	0.30
PFOS	0	-	
PFAS	3	1.01(0.70-1.46)	
Dose category			
Low	2	0.86(0.59-1.24)	0.02*
Medium	2	1.01(0.33-3.12)	
High	3	2.22(1.12-4.39)	

**denotes the p–value of test for linear trend.*

duration and level of exposure. Finally, we extracted the effect size measures, including relative risks (RRs), odds ratio (OR), risk ratio, rate ratio, standardized mortality ratio (SMR), or standardized incidence ratio (SIR), and their 95% Confidence Intervals (CI). If only results for subgroups were reported, we combined them using a fixed effect meta-analysis. If RR or CI were not reported, we calculated them from the row data if possible.

Eligible studies were critically appraised by two independent reviewers (MSS and PB) using a modified version of the Newcastle-Ottawa Scale (NOS) for case-control (6 items) and cohort studies (6 items) [15] (Supplementary Table 2). Studies that scored <8 corresponded to low quality, and those that scored >=8 were considered high quality.

2.2. Statistical Analysis

All analyses were completed using the STATA version 14.0 (Stata, College Station, TX, USA). We examined the exposure to PFAS and incidence and mortality from kidney, liver, and testicular cancer based on the RR and each study's corresponding 95% CIs. Heterogeneity (het.) among studies was evaluated by the Q test, based on the variation across studies rather than within studies, and the I2 statistic (the percentage of variance in a meta-analysis that is attributable to study heterogeneity) [16]. Random-effect models were used to account for heterogeneity in the design characteristics of the cohorts and case controls included in the meta-analysis [17].

First, we performed a meta-analysis, including non-overlapping studies for each cancer type separately. Then we conducted stratified analyses by geographic region (Europe, North America, others including Asia and Oceania), study design (cohort, nested case-control, case-control), level of exposure assessment (individual, ecologic), quality score (low, high quality), outcome (incidence, mortality), year of publication (<2014, >=2014), exposure source (occupational, environmental), and PFAS type (PFAS, PFOA, PFOS). In addition, we conducted a meta-regression of the RR on the quality scores.

We also abstracted dose-response results, including analyses by duration or level of exposure. We categorized results into low, medium, or high exposure. We conducted a meta-analysis of results in each category and a meta-regression of the linear trend using weights 1,2 and 4 for the exposure categories. Finally, we examined publication bias by creating a funnel plot and applying a regression asymmetry test [18].

3. Results

Based on our search of the literature and selection procedure, we included 15 independent

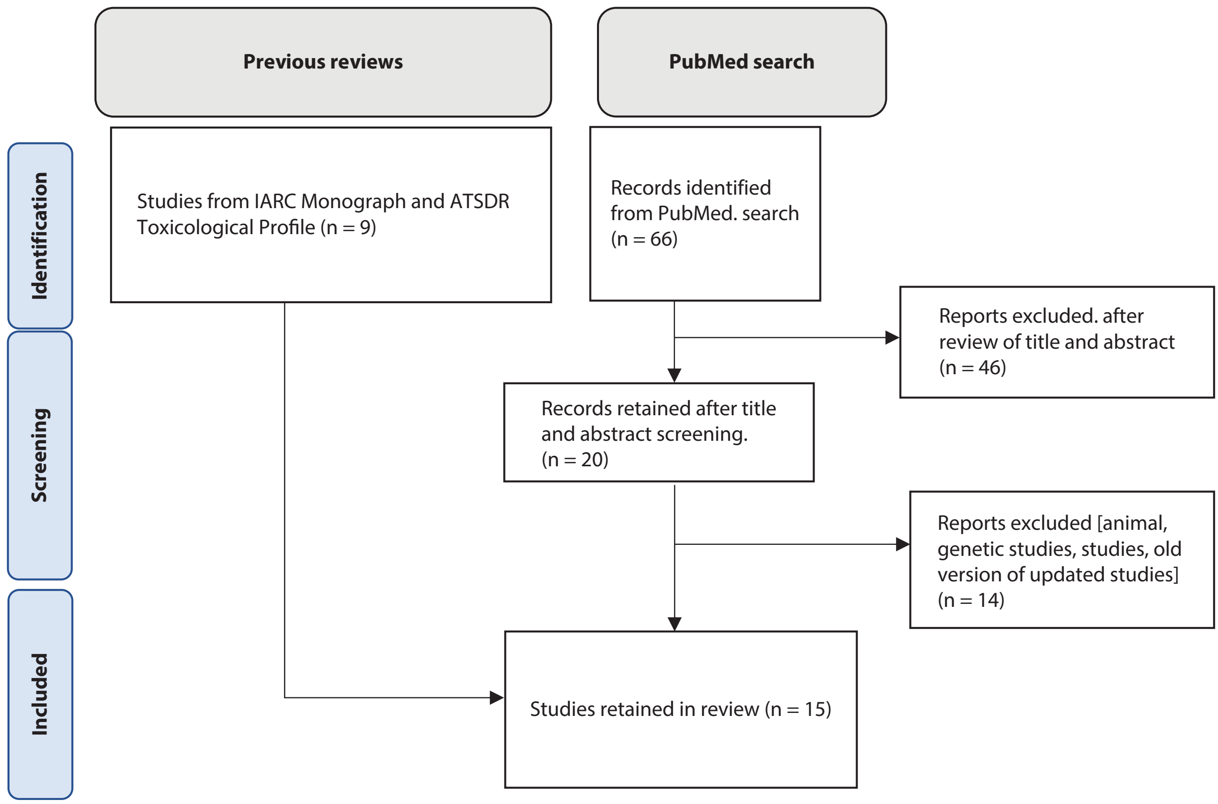


Figure 1. Selection of studies for inclusion in the review and meta-analysis.

studies in the review and meta-analysis [19-33]. The flow diagram for literature search and study selection is shown in Figure 1. The review comprised 10 cohort studies [19-21, 23, 25-28, 30, 33], three case-control studies nested in a cohort [22, 29, 32], and two case-control studies [24, 31]. All studies had individual-level assessments of PFAS exposure, except for two studies in which the assessment was ecologic-level [24, 27]. Details on these studies are provided in Supplementary Table 3.

The studies reported 11 risk estimates for kidney cancer [21, 23, 25-27, 29, 30, 33], 16 for liver cancer [20-24, 26, 27, 28, 30-33], and 8 for testicular cancer [19, 21, 23, 26, 27, 30, 33]. The summary RR of kidney cancer for ever-PFAS exposure was 1.18 (95% CI=1.05-1.32; I2=52.8%, p-het=0.02; Figure 2a). There was no association for liver (RR=1.03, 95% CI =0.91-1.16; I2=47.9%, p-het=0.02; Figure 2b) or testicular cancer (RR=1.12, 95% CI =0.94-1.34; I2 = 0.0%, p-het=0.52; Figure 2c).

The results of stratified meta-analyses are reported in Table 1. No differences by type of PFAS were detected for any of the cancers under review. Stratification by geographical region, study design, outcome, quality score, year of publication, quality score, and exposure source did not reveal heterogeneity for any of the three cancers under study. Stratification analysis by study design showed heterogeneity for kidney cancer (p=0.04) but not for liver and testicular cancer. The results of the meta-regression did not suggest a relationship between RR and quality score for kidney cancer (p=0.31), liver cancer (p=0.61), or testicular cancer (p=0.59). Only two studies reported results for women.

An analysis of stratification by low, medium, and high PFAS exposure showed an association between increased exposure and kidney (RR=1.74, 95% CI=1.23-2.47; p-trend=0.03) and testicular cancer (RR=2.22, 95% CI=1.12-4.39; p-trend=0.02), while the results for liver cancer did not reveal any trend (p= 0.37) (Supplementary Table 4).

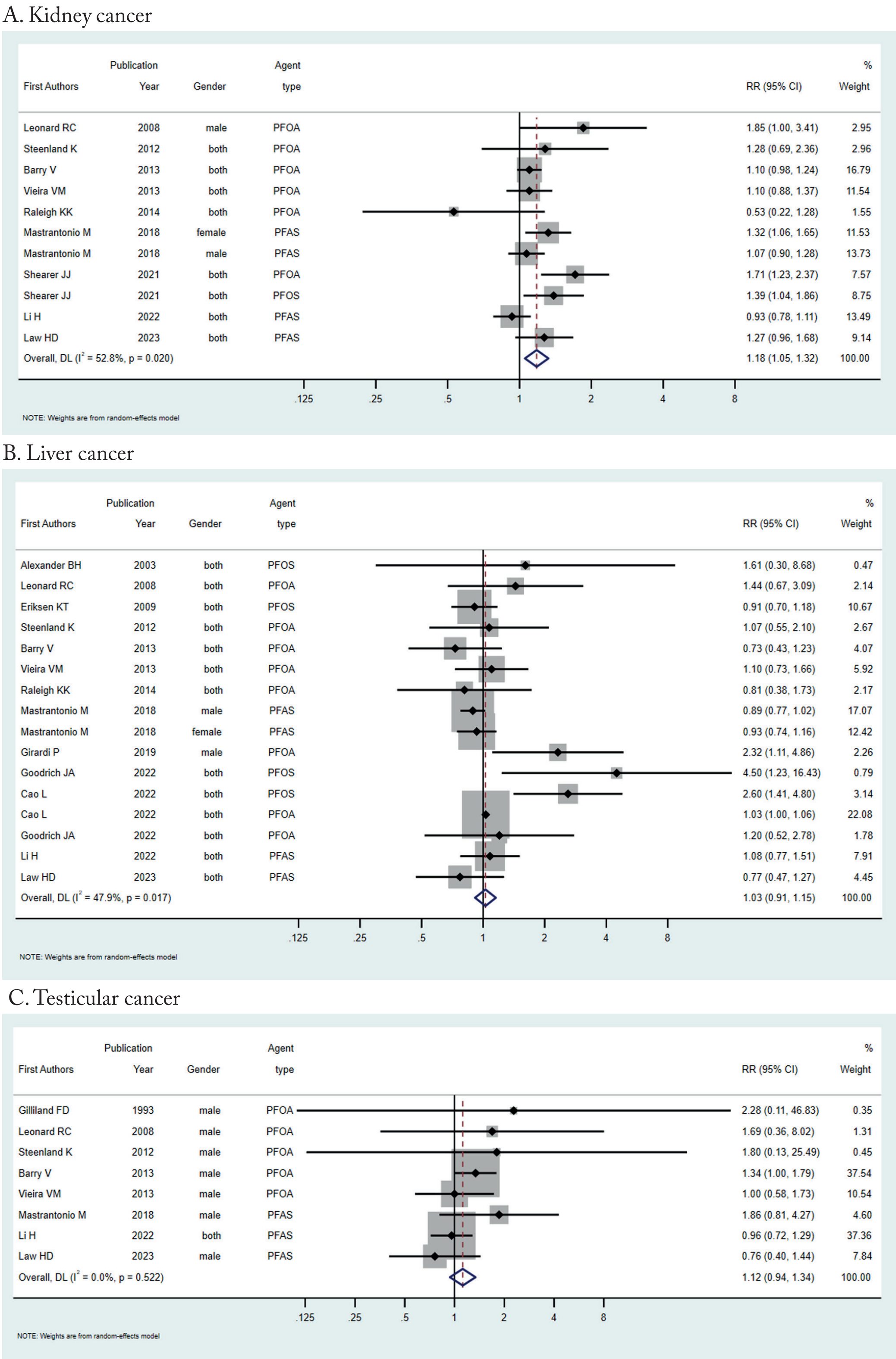
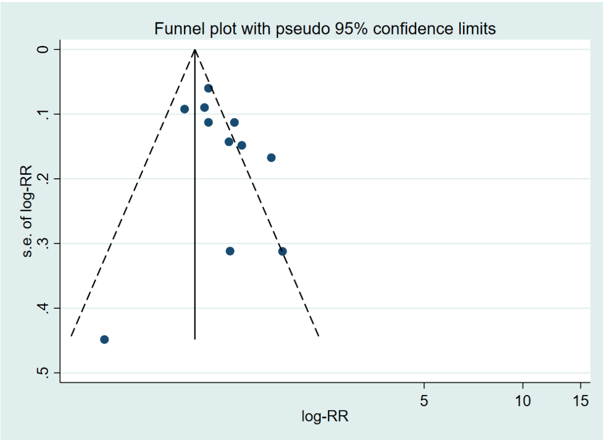
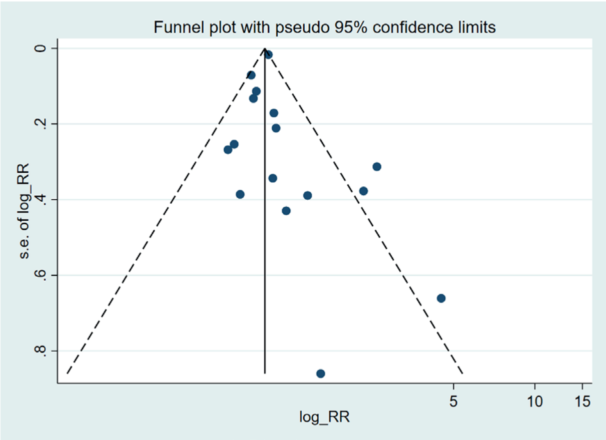


Figure 2. Forest plot (random-effects model) of results on the association between PFAS exposure and kidney, liver, and testicular cancer.

A. Kidney cancer



B. Liver cancer



C. Testicular cancer

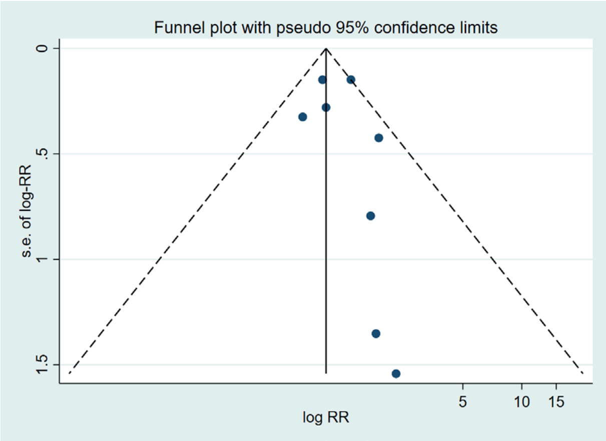


Figure 3. Funnel plot of results on the association between PFAS exposure and kidney, liver, and testicular cancer.

No publication bias was detected for kidney cancer (p=0.31), liver cancer (p=0.51), or testicular cancer (p=0.53); the funnel plots are shown in Figure 3.

4. Discussion

Our systematic review and meta-analysis presented an association between overall PFAS exposure and the risk of kidney cancer. Also, we found a dose-response relationship for kidney and testicular cancer. Conversely, we did not find an association with liver cancer.

The human body is exposed to PFAS through several sources and pathways, including ingestion through water, packaging materials, and food items; inhalation through air, and dermal absorption through various consumer products (e.g., waxes, leather, outdoor textiles, cosmetics, and impregnation spray) [9].

PFAS have a long half-life in the environment and inside the human body. It has been reported that the half-life of PFOA ranges from 2 to 3 years, whereas that of PFOS and other PFAS is longer, up to 4 to 7 years. This factor is associated with the amount of PFAS stored and the possible effects in different organs [34, 35]. The long half-life of these agents may explain that, despite a decrease in exposure over time in most populations, we did not find a difference in our analysis according to the year of publication [36].

When entering the body, this group of agents can affect it by various mechanisms [37]. PFAS are nephrotoxic through oxidative stress and epigenetic mechanisms linked to tubular reabsorption, leading to high concentrations in renal parenchyma [38, 39]. Also, the liver is an important storage organ for PFAS, which can lead to lipid metabolism alteration and non-alcoholic fatty liver disease, and ultimately to the subsequent development of cancer [40-42]. In addition, PFAS influences immunological processes and hormonal balance, resulting in possible reproductive effects on this group of organs in men and women [43-48].

Several confounding risk factors can affect the results of kidney, liver, and testicular cancer studies. Regarding liver cancer, major risk factors include chronic alcohol consumption, hepatitis B and C virus infection, tobacco smoking, and increased body mass. Concerning kidney cancer, it is critical to consider tobacco smoking, body size, hypertension, and other chronic kidney diseases [49]. In addition, perinatal exposures (such as maternal smoking) and medical conditions (cryptorchidism) are important risk factors for testicular cancer. There is also limited evidence that occupational exposures during firefighting and aircraft maintenance and environmental exposures, like that to organochlorine pesticides, may cause testicular cancer [50].

The results of the stratification analysis did not reveal any statistically significant heterogeneity. However, there was a suggestion of a stronger association between occupation exposure and testicular and liver cancer than environmental exposure. Workers are probably exposed to higher concentrations and more prolonged periods than the community exposed to environmental sources. Additionally, many factors affect the concentration of PFAS in water, soil, and food, such as seasonal rain levels, the use of private wells or tap public water, and geographical locations. However, regarding kidney cancer, this difference was not apparent. Results based on PFOS exposure suggested a stronger association with kidney and liver cancer risk compared to results based on PFOA or other unspecified PFAS. However, the difference was not statistically significant (no results were available on PFOS exposure and testicular cancer). Given the multiplicity of comparisons in the stratified analysis, these results should be interpreted cautiously. The analysis by geographic region revealed that few studies were conducted outside Europe and North America but did not show any consistent pattern.

There is some evidence that exposure to high doses of PFAS increases the risk of cancers like liver, testis, bladder, prostate, and breast. [7, 51] Despite the use of heterogeneous categories of exposure, which might have resulted in non-differential misclassification, our meta-regression suggested that high doses of PFAS are associated and seem to show a dose-response trend with kidney and testicular cancer but not liver cancer.

To our knowledge, this is the first systematic review and meta-analysis of studies dealing with the possible association between environmental and occupational PFAS exposure and liver, kidney, and testicular cancers. A severe limitation of our review is the relatively small number of available studies, particularly those addressing exposure to specific PFAS other than PFOA, those reporting results among female workers, and those conducted in countries outside North America and Europe, especially locations with a high prevalence of these cancers including East Asia and sub-Saharan Africa [11]. Thus, stratified analyses have limitations. The lack of adjustment for potential confounders is a severe drawback of many available studies.

In conclusion, we identified an association between overall PFAS exposure and kidney cancer and between high-dose exposure and kidney and testicular cancer. Residual confounding and other sources of bias prevent concluding the causal nature of these associations. Additional studies are needed to elucidate the carcinogenic risk from PFAS exposure fully.

Acknowledgments: The authors thank Germana Giupponi for assisting in identifying articles included in the review.

Conflicts of Interest: PB acted as an expert in litigation involving PFAS exposure unrelated to the present work. MSS declares no conflict of interest.

References

1. Ying L, Fletcher T, Mucs D, et al. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup Environ Med* 2018;75:46-51.
2. Gaines LGT. Historical and current usage of per- and polyfluoroalkyl substances (PFAS): A literature review. *Am J Ind Med.* 2023;66:353-378.
3. Exner M, Färber H. Perfluorinated surfactants in surface and drinking waters. *Environ Sci Pollut Res.* 2006:13;299-307.
4. Panieri E, Baralic K, Djukic-Cosic D, Buha Djordjevic A, Saso L. PFAS Molecules: A Major Concern for the Human Health and the Environment. *Toxics*. 2022;10:44.
5. European Environment Agency. 2019. Emerging chemical risks in Europe – PFAS. Copenhagen, EEA, 2019. [https://www.eea.europa.eu/themes/human/chemicals/emerging-chemical-risks-in-europe]
6. Fenton SE, Ducatman A, Boobis A, et al. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. *Environ Toxicol Chem*. 2021;40:606-630.

7. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. *Environ Res*. 2021;194:110690.
8. International Agency for Research on Cancer. PFOA. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, vol. 110. Some Chemicals Used as Solvents and in Polymer Manufacture. Lyon, IARC, 2017, pp. 37-110.
9. Ding N, Harlow SD, Randolph JF Jr, Loch-Caruso R, Park SK. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. *Hum Reprod Update*. 2020;26:724-752.
10. Chang ET, Adami HO, Boffetta P, Wedner HJ, Mandel JS. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. *Crit Rev Toxicol*. 2016;46:279-331.
11. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71:209-249.
12. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. Atlanta, GA, ATSDR, 2021.
13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-9.
14. Moher D, Liberati A; Tetzlaff J, Altmann DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009;151:264-69.
15. Stan, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603-605.
16. Higgins JP; Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002;21:1539-1558.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-88.
18. Egger M, Davey Smith G, Schneider M, Minder CE. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34.
19. Gilliland FD, Mandel JS. Mortality among employees of a perfluorooctanoic acid production plant. *J Occup Med.* 1993;35:950-4.
20. Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Environ Med*. 2003;60:722-9.
21. Leonard RC, Kreckmann KH, Sakr CJ, Symons JM. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. *Ann Epidemiol.* 2008;18:15-22.
22. Eriksen KT, Sørensen M, McLaughlin JK, et al. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. *J Natl Cancer Inst*. 2009;101:605-9.
23. Steenland K, Woskie S. Cohort mortality study of workers exposed to perfluorooctanoic acid. *Am J Epidemiol.* 2012;176:909-17.
24. Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environ Health Perspect*. 2013;121:318-23.
25. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect*. 2013;121:1313-8.
26. Raleigh KK, Alexander BH, Olsen GW, et al. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. *Occup Environ Med*. 2014;71:500-6.
27. Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. *Eur J Public Health*. 2018;28:180-185.
28. Girardi P, Merler E. A mortality study on male subjects exposed to polyfluoroalkyl acids with high internal dose of perfluorooctanoic acid. *Environ Res.* 2019;179:108743.
29. Shearer JJ, Callahan CL, Calafat AM, et al. Serum Concentrations of Per- and Polyfluoroalkyl Substances and Risk of Renal Cell Carcinoma. *J Natl Cancer Inst.* 2021;113:580-587.
30. Li H, Hammarstrand S, Midberg B, et al. Cancer incidence in a Swedish cohort with high exposure to perfluoroalkyl substances in drinking water. *Environ Res*. 2022;204:112217.
31. Cao L, Guo Y, Chen Y, Hong J, Wu J, Hangbiao J. Per-/polyfluoroalkyl substance concentrations in human serum and their associations with liver cancer. *Chemosphere*. 2022;296:134083.
32. Goodrich JA, Walker D, Lin X, et al. Exposure to perfluoroalkyl substances and risk of hepatocellular carcinoma in a multiethnic cohort. *JHEP Rep.* 2022;4:100550.
33. Law HD, Armstrong BK, D'este C, et al. Relative rates of cancers and deaths in Australian communities with PFAS environmental contamination associated withfire-fighting foams: A cohort study using linked data. *Cancer Epidemiol.* 2023;82:102296.
34. Li Y, Xu Y, Scott K, et al. Half-lives of PFOA, PFPeS, PFHxS, PFHpS and PFOS after end of exposure to contaminated drinking water. *Environ Epidemiol*. 2019;3:237.
35. Li Y, Fletcher T, Mucs D, et al. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup Environ Med*. 2018;75:46-51.
36. Brennan NM, Evans AT, Fritz MK, Peak SA, von Holst HE. Trends in the Regulation of Per- and Polyfluoroalkyl Substances (PFAS): A Scoping Review. *Int J Environ Res Public Health.* 2021;18:10900.

37. Fenton SE, Ducatman A, Boobis A, et al. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. *Environ Toxicol Chem*. 2021;40:606-630.
38. Wen LL, Lin CY, Chou HC, Chang CC, Lo HY, Juan SH. Perfluorooctanesulfonate mediates renal tubular cell apoptosis through PPARgamma inactivation. *PLoS One.* 2016;11:e0155190.
39. Stanifer JW, Stapleton HM, Souma T, Wittmer A, Zhao X, Boulware LE. Perfluorinated chemicals as emerging environmental threats to kidney health: A scoping review. *Clin J Am Soc Nephrol.* 2018;13:1479-1492.
40. Wan HT, Zhao YG, Wei X, Hui KY, Giesy JP, Wong CK. PFOS-induced hepatic steatosis, the mechanistic actions on beta-oxidation and lipid transport. *Biochim Biophys Acta*. 2012;1820:1092-1101.
41. Hui Z, Li R, Chen L. The impact of exposure to environmental contaminant on hepatocellular lipid metabolism. *Gene*. 2017;622:67-71.
42. Massoud O, Charlton M. Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and hepatocellular carcinoma. *Clin Liver Dis*. 2018;22:201-211.
43. Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Budtz-Jorgensen E. Serum vaccine antibody concentrations in adolescents exposed to perfluorinated compounds. *Environ Health Perspect*. 2017;125:077018.
44. Coperchini F, Awwad O, Rotondi M, Santini F, Imbriani M, Chiovato L. Thyroid disruption by perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). *J Endocrinol Invest*. 2017;40:105-121.
45. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect*. 2013;121:1313-1318.
46. Sabovic I, Cosci I, De Toni L, et al. Perfluorooctanoic acid impairs sperm motility through the alteration of plasma membrane. *J Endocrinol Invest*. 2020;43:641-652.
47. Cheng L, Albers P, Berney DM, et al. Testicular cancer. *Nat Rev Dis Primers*. 2018;4:29.
48. Di Nisio A, Rocca MS, Sabovic I, et al. Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. *Chemosphere*. 2020;242:125208.
49. Scelo G, Larose TL. Epidemiology and Risk Factors for Kidney Cancer. *J Clin Oncol.* 2018;36:3574-3581.
50. McGlynn KA, Trabert B. Adolescent and adult risk factors for testicular cancer. *Nat Rev Urol*. 2012; 9:339-49.
51. Imir OB, Kaminsky AZ, Zuo QY, et al. Per- and Polyfluoroalkyl Substance Exposure Combined with High-Fat Diet Supports Prostate Cancer Progression. *Nutrients*. 2021;13:3902.

Supplementary Material

Supplementary Table 1a. PRISMA Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P24
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5
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.	P5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5
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.	P5
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.	P5
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.	P5
	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.	P5
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.	P5
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.	P5

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)).	P6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P6
	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.	P6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P6
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.	P7,17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P17
Study characteristics	17	Cite each included study and present its characteristics.	P7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P7
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.	P7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P7
	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, describe the direction of the effect.	P7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P7

Table 1a (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P8
	23b	Discuss any limitations of the evidence included in the review.	P9
	23c	Discuss any limitations of the review processes used.	P9
	23d	Discuss implications of the results for practice, policy, and future research.	P9
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.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	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.	P1
Competing interests	26	Declare any competing interests of review authors.	P1
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.	NA

Supplementary Table 1b. PRISMA Abstract Checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

Supplementary Table 2. Modified Newcastle - Ottawa Quality Assessment Scale

Case Control Studies

1. **Selection of controls**
   a. From study base **(2)**
   b. Not from study base **(1)**
   c. Other, incl. ecological, no description **(0)**
2. **Adjustment of confounders**
   a. Adjustment for most important potential confounders **(2)**
   b. Adjustment for some potential confounders **(1)**
   c. Adjustment for no confounders except age, gender, race/ethnicity, calendar period **(0)**
3. **Ascertainment of exposure**
   a. Objective record (eg employment records, biomarkers) **(2)**
   b. Structured interview blind to case/control status, GIS **(1)**
   c. Interview not blinded to case/control status, self-report, proxy (e.g., residence) **(0.5)**
   d. No description **(0)**
4. **Response rate**
   a. Both groups over 90% **(2)**
   b. One or both groups between 60- 90% **(1)**
   c. One group under 60%, no description **(0)**
5. **Latency**
   a. Adequate latency between exposure and outcome (>15 yrs) (**2**)
   b. Limited latency between exposure and outcome (5-15 yrs) (**1**)
   c. Inadequate latency between exposure and outcome (<5 yrs), no description (**0**)
6. **Outcome**
   a. Cancer registration (**2**)
   b. Death certificates, hospital records (**1**)
   c. Self report (**0.5**)
   d. No description (**0**)

Cohort Studies

1. **Selection of unexposed cohort**
   a. Derived from the same population as the exposed **(2)**
   b. Derived from a different source **(1)**
   c. Other, no description **(0)**
2. **Adjustment of confounders**
   a. Adjustment for most important potential confounders **(2)**
   b. Adjustment for some potential confounders **(1)**
   c. Adjustment for no confounders except age, gender, race/ethnicity, calendar period **(0)**
3. **Ascertainment of exposure**
   a. Objective record (e.g., employment records, biomarkers) **(2)**
   b. Structured interview blind to outcome status, GIS **(1)**
   c. Interview not blinded outcome status, self-report, proxy (e.g., residence) **(0.5)**
   d. No description **(0)**
4. **Follow-up rate**
   a. Follow-up of both groups over 90% **(2)**
   b. Follow-up of one or both groups between 60- 90% **(1)**
   c. Follow-up of one group under 60%, no description **(0)**
5. **Latency**
   a. Adequate latency between exposure and outcome (>15 yrs) (**2**)
   b. Limited latency between exposure and outcome (5-15 yrs) (**1**)
   c. Inadequate latency between exposure and outcome (<5 yrs), no description (**0**)
6. **Outcome**
   a. Cancer registration (**2**)
   b. Death certificates, hospital records (**1**)
   c. Self report (**0.5**)
   d. No description (**0**)

Supplementary Table 3. Selected characteristics of the studies included in the review and meta-analysis.

Ref. #	1st author and year	Study design	Gender*	Cancer type	Country	Type of PFAS	Exposure source	Potential confounders included in the analysis (other than sex, age, calendar period)	Quality score
19	Gilliland FD, 1993	Cohort	Male	Testis	USA	PFOA	Occupational		8
20	Alexander BH, 2003	Cohort	Both	Liver	USA	PFOS	Occupational		6
21	Leonard RC, 2008	Cohort	Both	Liver, kidney, testis	USA	PFOA	Occupational		6.5
22	Eriksen KT, 2009	Nested case-control	Both	Liver	Den-mark	PFOA, PFOS	Environmental	Tobacco smoking, education, alcohol drinking, occupation	11
23	Steenland K, 2012	Cohort	Both	Liver, kidney, testis	USA	PFOA	Occupational		7
24	Vieira VM, 2013	Case-control ecologic	Both	Liver	USA	PFOA	Environmental		7
25	Barry V, 2013	Cohort	Both	Kidney	USA	PFOA	Environmental		8.5
26	Raleigh KK, 2014	Cohort	Both	Liver, kidney, testis	USA	PFOA	Occupational		10
27	Mastrantonio M, 2018	Cohort ecologic	Both	Liver, kidney, testis	Italy	PFAS	Environmental		6.5
28	Girardi P, 2019	Cohort	Male	Liver	Italy	PFOA	Occupational		8
29	Shearer JJ, 2021	Nested case control	Both	Kidney	USA	PFOA, PFOS	Environmental	BMI, tobacco smoking, hypertension	12
30	Li H, 2022	Cohort	Both	Liver, kidney, testis	Sweden	PFAS	Environmental		7.5
31	Cao L, 2022	Case control	Both	Liver	China	PFOA, PFOS	Environmental	Education, BMI, income, tobacco smoking, medical history	6
32	Goodrich JA, 2022	Nested case control	Both	Liver	USA	PFOA, PFOS	Environmental		11
33	Law HD, 2023	Cohort	Both	Liver, kidney, testis	Australia	PFAS	Environmental	Adjusted for age, sex and calendar period	6.5

** Male: >75% male; both: neither gender >75%*
BMI, body mass index

Supplementary Table 4. Results on dose-response relationship.

First Author, year	Exposure level	Dose detail	RR (95% CI)	PFAS type	Cancer type
Alexander BH (2003)	High	N/A	2.00 (0.05-11.10)	PFOS	Liver
	Low	N/A	3.94 (0.1-21.88)		
Girardi P (2019)	High	> 16,956 ng /mL-years	3.07 (1.15-8.18)	PFOA	Liver
	Medium	4034–16,956 ng/mL-years	2.76 (0.69-11.00)		
	Low	≤4,034 ng/mL-years	1.02 (0.12-7.21)		
Shearer JJ (2021)	High	>7.3-27.2 μg /-l	2.63 (1.33-5.20)	PFOA	Kidney
	Medium	>5.5-7.3 μg /-l	1.24 (0.64-2.41)		
	Low	≥4-5.5 μg /l	1.47 (0.77-2.80)		
	High	>49.9-154.2 μg /-l	2.51 (1.28-4.92)	PFOS	
	Medium	>38.4-49.9 μg /-l	0.92 (0.45-1.88)		
	Low	>26.3-38.4 μg /-l	1.67 (0.84-3.30)		
Li H (2022)	High	N/A	1.07 (0.75-1.54)	PFAS	Kidney
	Low	N/A	0.88 (0.72-1.09)		
	High	N/A	0.98 (0.45-1.86)		Liver
	Low	N/A	1.12 (0.72-1.66)		
	High	N/A	1.28 (0.70-2.15)		Testis
	Low	N/A	0.85 (0.57-1.21)		
Raleigh KK (2014)	High	>7.9×10 – 4 μg/m3 years.	0.73 (0.21-2.48)	PFOA	Kidney
	Medium	2.9×10-5 - 1.5×10-4 μg /m3 years	1.07 (0.36-3.17)		
	Medium	1.5×10-4 - 7.9×10-4 μg /m3 years.	0.98 (0.33-2.92)		
	Low	<2.9×10-5 μg /m3 years	1.07 (0.36-3.16)		
	High	>1.5×10-4 μg /m3 years	0.67 (0.14-3.27)		Liver
	Low	<1.5×10-4 μg /m3 years	2.09 (0.69-6.31)		
Eriksen KT (2009)	Low	N/A	0.62 (0.29-1.33)	PFOS	Liver
	Medium	N/A	0.72 (0.33-1.56)		
	High	N/A	0.59 (0.27-1.27)		
	High	N/A	0.60 (0.26-1.37)	PFOA	
	Low	N/A	1.00 (0.44-2.23)		
Steenland K (2012)	High	≥2,700 ppm-years	2.66 (1.15-5.24)	PFOA	Kidney
	Medium	904–<1,520 ppm-years	1.37 (0.28-3.99)		
	Low	0–<904 ppm-years	1.07 (0.02-3.62)		
	High	≥2,700 ppm-years	0.32 (0.01-1.76)		Liver
	Medium	1,520–<2,700 ppm-years	2.01 (0.65-4.68)		
	Low	0–<904 ppm-years	2.39 (0.65-6.13)		

Table 4 (*Continued*)

First Author, year	Exposure level	Dose detail	RR (95% CI)	PFAS type	Cancer type
Vieira VM (2013)	High	110–655 µg/L	2.8 (0.8-9.2)	PFOA	Testis
	Medium1	12.9–30.7 µg/L	0.6(0.2-2.2)		
	Medium2	30.8–109 µg/L	0.3 (0-2.7)		
	Low	3.7–12.8 µg/L	0.2 (0-1.6)		
	High	30.8–109 µg/L	1.0 (0.3-3.1)		Liver
	Medium1	12.9–30.7 µg/L	0.9 (0.3-2.5)		
	Low	3.7–12.8 µg/L	1.1 (0.4-1.5)		
	High	110–655 µg/L	2.0 (1.0-3.9)		Kidney
	Medium1	12.9–30.7 µg/L	1.2 (0.7-2.0)		
	Medium2	30.8–109 µg/L	2.0 (1.3-3.2)		
	Low	3.7–12.8 µg/L	0.8(0.4-1.5)		
Barry V (2013)	High	N/A	1.58 (0.88-2.84)	PFOA	Kidney
	Medium	N/A	1.48 (0.84-2.60)		
	Low	N/A	1.23 (0.70-2.17)		
	High	N/A	3.17 (0.75-1.45)		Testis
	Medium	N/A	1.91 (0.47-7.75)		
	Low	N/A	1.04 (0.26-4.22)		

La Medicina del Lavoro

Original article

Med Lav 2023; 114 (5): e2023038
DOI: 10.23749/mdl.v114i5.14927

Mesothelioma Risk Among Maritime Workers According to Job Title: Data From the Italian Mesothelioma Register (ReNaM)

Luigi Vimercati[1,*], Domenica Cavone[1], Omero Negrisolo[2], Floriana Pentimone[1], Luigi De Maria[1], Antonio Caputi[1], Stefania Sponselli[1], Giuseppe Delvecchio[1], Francesco Cafaro[1], Elisabetta Chellini[3], Alessandra Binazzi[4], Davide Di Marzio[4], Carolina Mensi[5], Dario Consonni[5], Enrica Migliore[6], Carol Brentisci[6], Andrea Martini[7], Corrado Negro[8], Flavia D'Agostin[8], Iolanda Grappasonni[9], Cristiana Pascucci[9], Lucia Benfatto[10], Davide Malacarne[10], Veronica Casotto[11], Vera Comiati[11], Cinzia Storchi[12], Lucia Mangone[12], Stefano Murano[13], Lucia Rossin[13], Federico Tallarigo[14], Filomena Vitale[14], Marina Verardo[15], Silvia Eccher[16], Gabriella Madeo[17], Tommaso Staniscia[18], Francesco Carrozza[19], Ilaria Cozzi[20], Elisa Romeo[20], Paola Pelullo[21], Michele Labianca[22], Massimo Melis[23], Giuseppe Cascone[24], Giovanni Maria Ferri[25] and Gabriella Serio[26]

[1]Section of Occupational Medicine "B. Ramazzini", Department of Interdisciplinary Medicine, Regional Operating Center of Puglia (COR Puglia), University of Bari, Bari, Italy
[2]Environmental Prevention Technician former Judicial Police Officer Padua, Italy
[3]Occupational physician, Florence, Italy
[4]Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Italian Workers' Compensation Authority (INAIL), Rome, Italy
[5]Epidemiology Unit, Regional Operating Center of Lombardia (COR Lombardia), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[6]Unit of Cancer Epidemiology, Regional Operating Center of Piemonte (COR Piemonte), University of Turin and CPO-Piemonte, Turin, Italy
[7]Prevention and Clinical Network, Institute for Cancer Research, Regional Operating Center of Tuscany (COR Toscana), Florence, Italy
[8]Clinical Unit of Occupational Medicine, Regional Operating Center of Friuli-Venezia Giulia (COR Friuli-Venezia Giulia), University of Trieste-Trieste General Hospitals, Trieste, Italy
[9]Regional Operating Center of Marche (COR Marche), School of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy
[10]Regional Operating Center of Liguria (COR Liguria Regional Operating Center of Liguria (COR Liguria), Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[11]Azienda Zero, Epidemiological Department, Regional Operating Center of Veneto (COR Veneto), Veneto Region, Padua, Italy
[12]Epidemiology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[13]Occupational Medicine Unit, Alto Adige Health Authority, Regional Operating Center of Autonomous Province of Bolzano (COR A.P. of Bolzano), Bolzano, Italy
[14]Public Health Unit, Regional Operating Center of Calabria (COR Calabria), Crotone, Italy
[15]Valle d'Aosta Health Local Unit, Regional Operating Center of Valle d'Aosta (COR Valle d'Aosta), Aosta, Italy
[16]Hygiene and Occupational Medicine, Provincial Unit of Health, Regional Operating Center o Autonomous Province of Trento (COR A.P. of Trento), Trento, Italy
[17]Center of Umbria (COR Umbria), Servizio Prevenzione, Sanità Veterinaria e Sicurezza Alimentare-Regione Umbria, Perugia, Italy
[18]COR Abruzzo, Abruzzo Regional Health Agency (ASR), Pescara, Italy
[19]Oncology Unit, Cardarelli Hospital, Regional Operating Center of Molise (COR Molise), Campobasso, Italy
[20]Regional Operating Center of Lazio (COR Lazio), Department of Epidemiology, Epidemiology Lazio Regional Health Service, ASL Roma 1, Rome, Italy
[21]Department of Experimental Medicine, "Luigi Vanvitelli" University, Regional Operating Center of Campania (COR Campania), Naples, Italy

[22]Epidemiologic Regional Center, Regional Operating Center of Basilicata (COR Basilicata), Potenza, Italy
[23]Regional Epidemiological Center, Regional Operating Center of Sardegna (COR Sardegna), Cagliari, Italy
[24]Regional Operating Center of Sicilia (COR Sicilia), ASP Ragusa Dip. Prevenzione Medica, Ragusa, Italy
[25]Occupational physician, Bari, Italy
[26]Department of Emergency and Organ Transplantation (DETO), Pathological Anatomy Section, University of Bari Aldo Moro, Bari, Italy

Keywords: Mesothelioma; Seamen; Asbestos; Navy; Merchant Marine; National Mesothelioma Register

Abstract

Background: *The study describes the 466 cases of malignant mesotheliomas (MM) collected by the National Mesothelioma Register (ReNaM) in Italy from 1993-2018 relating to subjects with exclusive asbestos exposure in merchant or military navy.* **Methods:** *The cases among maritime workers represent 1.8% of the total patients with defined exposure registered in the ReNaM, of which (45.4%) were among merchant maritime workers and 254 cases (54.5%) among the navy. The distribution by site of mesothelioma showed 453 (97.2%) MM cases of the pleura, 11 (2.3%) of the peritoneum, and 2 (0.4%) of the tunica vaginalis of the testis. With regard to occupational exposure, it was classified as certain in 318 (68.2%) cases, probable in 69 (14.8%) cases, and possible in 79 (16.9%) cases.* **Results:** *Among the 23 classified jobs, the highest percentages of certain exposures are among naval engineers, motor mechanics, machine captains, and sailors. Machine crew accounted for 49.3% of the cases, and deck crew for 27.6%. All cases began exposure on board between 1926 and 1988. Seamen were exposed to asbestos while at sea by living onboard ships and from the continual release of asbestos fibers due to the motion of a vessel.* **Conclusions:** *Epidemiological surveillance through the ReNaM has allowed us to verify among cases in the maritime, navy, and merchant marine sectors that, in the past, subjects were exposed regardless of the ship's department where they have provided service; therefore, all these cases must be considered occupational diseases.*

1. Introduction

Malignant Mesothelioma (MM) is a rare and lethal cancer of the pleura, peritoneum, pericardium, and tunica vaginalis testis caused by asbestos, the main etiologic agent of this cancer. This cancer has a long latency, and there is no known safe level of asbestos exposure [1].

Asbestos was widely used in industry in the last century, including shipbuilding. The use of asbestos in both merchant and military vessels in the past has been extensive and well-documented. It has been used in the compact and friable forms, mainly for thermal insulation of structures and pipelines for fluids, fire protection, sound absorption, anti-condensation, soundproofing, insulation, and other products used on board ships [2-6].

From the early 1930s to the mid to late 1970s, naval and commercial shipyards used hundreds of tons of asbestos, primarily chrysotile and amphiboles asbestos-containing insulation, to build and repair maritime vessels. For example, warships contained roughly 30 and 500 tons of asbestos insulation on bulkheads, pipes, and machinery [2, 7, 8].

Hollins (2009) and Franke (2011), in their reviews, reported that since the 1880s up to the 70s and beyond, at least until 1978-1980, amosite and chrysotile asbestos fiber type, and lesser extent crocidolite, were used extensively as insulating materials on naval ships. In the 1930s, the U.S. (United States)

Received 16.06.2023 – Accepted 12.07.2023
*Corresponding Author: Luigi Vimercati, E-mail: luigi.vimercati@uniba.it

Navy also approved using amosite that was required in many military specifications for insulation and other materials on ships. Asbestos-containing products on ships included joiner bulkhead systems in living spaces, insulation on both hot water and steam piping, inside and outside of boilers and cold-water pipes to avoid condensation, tanks, and also in machinery casings, block insulation, asbestos cement, and lagging, pre-formed asbestos insulation, flanges and valves, and vinyl asbestos tile for decking and flooring.

Asbestos was sprayed onto deck heads, bulkheads, and the inside face of the hull, pipes, and machinery were insulated with molded sections containing asbestos. Asbestos was applied in rooms and on installations inside and outside the engine rooms, so potentially the entire crew could have been at risk [3-4].

Although chrysotile was most commonly applied aboard, suspended brown asbestos was detected inside and outside the engine room on a frigate, brown asbestos was also found aboard Norwegian civilian vessels inspected during the 1970s [2].

It has been hypothesized that vibrations during sailing would release asbestos fibers to the breathing atmosphere in most areas aboard or from insulation repairs conducted during travel at sea, including ruptures, failures, or blowouts on the steam piping. In submarines, active handling of asbestos was predominantly limited to the engine rooms, but the closed environment during submerged might have put all crew at risk. Onboard operations such as inspections, maintenance, repair, and refitting would involve contact with asbestos for crew members. Seamen were exposed to asbestos in-place, as environmental asbestos exposure, continually due to their living onboard ships and the continual release of asbestos fibers due to the vessel motion. Moreover, structural corrosion caused by salt water and air could facilitate the clearance of asbestos from its supporting matrix [5, 9, 10].

Franke (2011) studied U.S. Government and Navy knowledge regarding the health hazards of asbestos between 1900 to 1970. He stated that the Navy continued to require asbestos-containing materials on ships but recommended that proper precautions be taken when handling asbestos. Nevertheless, until 1970, neither the military nor the private sector believed that the myriad of asbestos-containing products considered "encapsulated" (e.g., gaskets, brakes, bakelite) would have posed a health hazard to those working with them. The Navy attempted to control exposures to concentrations that it considered acceptable. It began looking for substitute materials during the 1970s, and most uses ceased by about 1985 [4].

Among the first scientific publications indicating probable asbestos exposure-related effects in a population of seamen it must be mentioned those by Jones (1984) Velonakis (1989), and Selikoff (1990) [11-13] that reported radiological anomalies in merchant marine seamen and American marine engineers. The prevalence of asbestosis changes differed in seamen who served in different ship departments, deck, engine room hands, bargemen, light tenders and boatmen, engineering and radio officers, pilots ships and foremen, lighters, and other vessel crew. Darby (1990) [14] reported an excess of deaths in the British Royal Navy. The association between occupational seafaring and excess risk of mesothelioma has been reported in numerous studies, many sand studies on seafarers conducted in the Nordic countries. Nordic seafarers on merchant vessels had an overall increased risk of pleural cancer, and an excess of mesotheliomas was described among Finnish machinists, engine room crews, and deck crew, but also among seamen in Denmark, Norway, Sweden, and Iceland [15-29]. The same findings were described among merchant marine seamen and U.S. Navy [30]. More recently, a series of studies conducted on seamen from the Nordic countries [31] studied incidence, mortality, and survival in malignant pleural mesothelioma before and after the asbestos ban in Denmark, Finland, Norway, and Sweden and found that in these countries, the male incidence trends for MM climaxed and started to decrease, indicating that the prevention of exposure was beneficial. The same results were reported by Forsell (2022) [32] on cancer incidence between 1985 and 2011 in a Swedish seafarer's cohort. A significant decreasing trend for cancer risk was found. Increased risks of cancer in seafarers reported in the literature stem primarily from older periods of seafaring up to 1999 at the latest [16, 20, 23, 25]. Petersen (2020), in a study among seafarers employed on Danish ships during 1986-1999, reported that among seafarers with first employment before 1992, the overall mortality was high; this excess in mortality was evident primarily among non-officers on board tankers and smaller ships [24].

Excess mortality from mesothelioma was recently reported by Boice (2020) and Till (2022) [33-34] among atomic veterans; it was explained by asbestos exposure among enlisted naval personnel. The sources of exposure were determined to be on navy ships in areas (or with materials) with known asbestos content.

Regarding Italy since 1992, Rapiti [35], in a cohort of more than 2000 seamen, found an increased risk of respiratory cancer among subjects with an occupational history of sailing, possibly due to past asbestos exposure. In a study of mesothelioma in the Trieste Province, between 1968 and 1987, 19 cases (11.2%) were reported for various trades of seamen in the Navy and merchant marine including machinist (9), Navy official (4), cook (2), electrician (2), cabin-boy (1) and steward (1) [36].

Bianchi (2005) [37] reviewed pleural mesotheliomas diagnosed in the Trieste-Monfalcone area among seamen in 1973-2003; they had served in the Italian Navy, in the Merchant Navy, or both and showed long latency periods. The author stated that mesothelioma in seamen should be considered an occupational disease. Mensi (2006) [38] reported eleven cases of mesothelioma among Italian navy personnel (stokers, bomb squad, electrical maintenance man, gunners, and simple sailors). Larese Filon (2013) [39] reported that mesothelioma in seamen and marine engineers represented about 2.5% of the overall Italian mesothelioma cases with a very long latency period (47.6 +/- 9.6 years).

The International Convention for the Safety of Life at Sea (SOLAS) has banned the use of asbestos or materials containing asbestos on merchant ships worldwide only since 1 January 2011. Therefore, due to the recognized long latency time of the onset of mesothelioma, asbestos remains a serious public health concern in the maritime sector. Moreover, possible asbestos exposure could still occur where, more or less accidentally, on asbestos-free ships, spare parts containing asbestos were installed during maintenance. These components are still produced and sold in several countries around the world. Considering the high number of workers employed, studying and monitoring exposure to asbestos in the maritime sector is crucial. The most recent available Italian data report that in the maritime transport sector, on average yearly, 42,348 units are employed (ISTAT 2020 last accessed 3 April 2023 http://dati.istat.it/index.aspx?queryid=20596). Meanwhile, in the Navy sector, there are 29,567 units engaged by the Navy as of 31/12/2021 (https://www.difesa.it/Amministrazionetrasparente/persomil/Documents/PERSONALE/Conto_annuale_2021/02_Conto_MM.pdf last accessed 3 April 2023).

Therefore, this study aims to describe the cases on MM collected by ReNaM in 1993-2018 relating to subjects with exclusive asbestos exposure in merchant or military Navy, military or merchant seamen workers.

2. Methods

Data were collected by ReNaM, a national epidemiological surveillance system characterized by a network of regional operating centers ('Centri Operativi Regionali': COR) established in all Italian regions using a systematic active search of MM over the entire national territory with standard criteria for active case search, diagnosis classification, and qualitative assessment of asbestos exposure obtained occupational and residential histories of exposure and lifestyle habits by interviewing affected subjects (or next of kin) through a standardized questionnaire. Asbestos exposure was categorized as occupational" (with three degrees of certainty: "definite", "probable", "possible") or "non-occupational" (in-house, environmental, and other non-occupational–such as leisure-time-related activities). "Unlikely"exposure was assigned to subjects whose information was inadequate or asbestos exposure could be reasonably ruled out [40].

Subjects with occupational exposure exclusively in the maritime sector (codes 75.22 and 61 of the Italian classification of economic activities' ATECO 1991') [41] were analyzed. In this study, we did not consider the workers of the fisheries (ATECO code 05) nor those of the military arsenals or shipyards (ATECO code 35).

The occupational codes of the Italian classification of economic activities 'ATECO 1991' and the Classification of ISTAT Professions 1991 [42] were based upon the salaried reporting system of the industry to which each examinee belonged. For each case, it was used the ISTAT codes of professions of the national ReNaM database integrated with the notes on the jobs and on the ships where the subject has been embarked if present in the same database.

We converted the ISTAT codes ('ATECO 91') into the maritime sector's, reported tasks and professional qualifications of seafarers, both as the Code of Navigation, concerning the regulation of professional titles and as Collective Agreement National Work for the Private Sector of The Shipping Industry [43, 44] to examine homogeneous groups of people exposed. "Maritime work" means any work activity on board a ship at sea or in port. Anyone who performs "maritime work" usually belongs to a specific category of workers called "people of the sea". Maritime work as a civilian activity occurs in three sectors: transport, fishing, and yachting. As far as transport is concerned, this refers to the work performed on board ships used for the transport of goods and passengers, "beyond straits" on the oceanic routes of international traffic, on "short" routes of national and Mediterranean cabotage, and onboard special vessels operating "offshore", for laying pipelines, the construction and installation of platforms, etc., as well as onboard service vessels in ports, such as tugs, pilot units, vessels involved in bunkering, i.e., at refueling, etc. As far as pleasure boating is concerned, it is working on board boats designed for sporting or recreational purposes from which the pursuit of profit does not exist, but which the law allows that they can also be employed in economic activities, for commercial purposes, through contracts of lease and rental ("nautical charter") or for teaching pleasure boating, as well as a support unit for scuba diving for sporting or recreational purposes. The maritime personnel recognized by the harbor master's offices are deck personnel, engine personnel, multi-skilled personnel, health personnel, room personnel, kitchen, and household personnel, and personnel assigned to various services. Each category includes a large number of jobs and qualifications. For the navy, regardless of military rank (admiral, ship captain, ship lieutenant, midshipman, marshal, sergeant, graduates, enlisted men and soldiers without rank or cadets) and of the navy corps to which they belong) general staff, navy engineers (naval weapons, naval engineering, infrastructures), medical units, maritime military commissariat, port authorities, maritime military crews) from the point of view of the occupational risk of asbestos exposure, the various jobs can be considered to overlap with those of the merchant marine (Table 1 supplementary material).

Some maritime, military, and merchant workers performed more than one task because, during their professional careers, they had promotions or changed jobs and qualifications, which resulted in 1451 circumstances of asbestos exposure. Among these, we have excluded those who, for example, had a period of exposure due to military service in the Navy. Only 466 subjects with exclusive navy or merchant marine exposure were considered and analyzed jointly. The 49 jobs among navy workers and 51 among merchant marine workers were classified as shown in Table 2 supplementary material.

Qualitative assessment of retrospective exposure is key in identifying subjects exposed to asbestos and examining the association between asbestos exposure and mesothelioma occurrence [45]. Quantitative data on asbestos exposure, i.e., information about measurement (fibers/cm^3) at the workplace for any subjects, are not available in the ReNaM database. The exposure level for the analyses was attributed to certain, probable, and possible following the qualitative classification of exposure as reported in the ReNaM guidelines based on responses and information collected from the patient through a standardized questionnaire evaluated by industrial hygienists [40] and in agreement with the literature [2-5, 10].

- Certain occupational exposure was attributed to subjects who used asbestos or materials containing asbestos.
- Probable occupational exposure was attributed to subjects who had worked in a firm where asbestos was used but whose exposure could not be documented together with the frequency of direct or bystander asbestos exposure.

- Possible occupational exposure was attributed to subjects who had worked in an economic sector where asbestos had been used together with the frequency of direct or bystander asbestos exposure, such as typical tasks, work practices, and materials used over time.

The data analyzed refer to the incidence period 1993-2018. Descriptive analysis has been performed: mean and the median age at diagnosis, mean and the median age at the beginning of exposure, mean and median duration of exposure, and mean and median latency by morphology were calculated with their Standard Deviation using STATA 12 software (College Station, TX: StataCorp L.P.). The first asbestos exposure was considered to have coincided with the start of employment in the job during which the initial asbestos exposure had occurred. Similarly, the duration of asbestos exposure was approximated by duration of employment in the job with probable or definite asbestos exposure. The latency period was defined as the period between the first exposure to asbestos and the certified diagnosis of MM calculated for each maritime worker job. The distribution of cases by job, qualitative exposure to asbestos, period of exposure beginning (1926-1960; 1961-1988), and period of incidence (1993-2000, 2001-2010, 2011-2018) are shown too.

3. Results

The 466 cases among maritime workers, as first defined, represent 1.8% of the total cases with defined exposure registered between 1993 and 2018 in Italy [46], of which 212 (45.4%) cases among merchant maritime workers and 254 (54.5%) cases among navy. Among the cases with exclusive exposure in the military defense category ReNaM code economic categories 35, the 254 subjects exposed in the navy represent 66.6%of the cases [46]. Among the cases with exposure in the ReNaM code economic categories 30 maritime transport category, the 212 exposed subjects with exclusive exposure represent 47.4% of the cases [46].

The 466 cases were all male subjects except one female of the navy in charge of surveillance. The distribution by site of mesothelioma showed 453 (97.2%) MM cases of the pleura, 11 (2.3%) of the peritoneum, and 2 (0.4%) of the tunica vaginalis of the testis. In terms of diagnostic certainty, there were 383 (82.1%) certain, 43 (9.2%) probable, and 40 (8.5%) possible mesotheliomas. Regarding histotype, it was epithelioid for 285 (61.1%) cases, sarcomatous in 37 (7.9%) cases, biphasic in 45 (9.6%) cases, malignant in 51 (10.9%) cases and undefined in 48 (10.3%). With regard to occupational exposure, it was classified as certain in 318 (68.2%) cases, probable in 69 (14.8%) cases, and possible in 79 (16.9%) cases [40]. Mean age at diagnosis was 71.9 years SD 9.5 median 76 range (36-96), mean age at the beginning of exposure was 20.7 years SD 4.8 median 20 range (14-55), mean duration of exposure was 20.8 years SD 15.2 median 20 range (1-58), mean latency was 55.6 years SD 10.5 median 52 range (17-82).

The 11 cases of peritoneal MM were all male with a mean age at diagnosis of 63.45 years SD 15.18, the beginning of exposure in the years between 1936 and 1984 and age at the beginning of exposure between 17 and 23 years, average duration of exposure 16.81 years SD 12.69, mean latency 44.09 years SD 15.51. Five had been exposed in the merchant marine and 6 in the navy. The jobs were a helmsman on merchant ships, a submarine commander, and nine naval engineers, including 5 in the navy and 4 in the merchant marine.

The two cases of TVT MM with age at the beginning of exposure, both of 20 years, started respectively in 1976 and 1941, duration of exposure of 2 and 4 years, age at diagnosis of 46 and 82 years, and latency of 26 and 62 years. Both subjects were exposed in the Navy as a ship electrician and a tugboat pilot.

Concerning the task, 49.3% of the cases belonged to the machine crew and 27.6% to the deck crew (Table 1).

Among the 23 classified jobs, the highest percentages of certain exposures in descending order are among naval engineers, motor mechanics, machine captains, and sailors, the most represented jobs among the 466 cases (totaling 285 cases equal to 61.1% of all cases). In 21 jobs, except for the two classified as various services boards and various services on services, over 50% of the patients had certain exposure (Table 2).

Table 1. Distribution of cases (number and percentage) by task and qualitative exposure assigned.

TASK number	Exposure			Total (%)
	Certain (%)	Probable (%)	Possible (%)	
1. Meck Crew	67 (51.9)	27 (20.9)	35 (27.1)	129 (100)
2. Medical Staff on Board	-	-	-	-
3. Various Service Crew	47 (62.6)	15 (20.0)	13 (17.3)	75 (100)
4. Room Family Kitchen Crew	14 (53.8)	8 (30.7)	4 (15.3)	26 (100)
5. Local Traffic Crew	3 (50.0)	1 (16.6)	2(33.3)	6 (100)
6. Machine Crew	187 (81.3)	28 (12.1)	15 (6.5)	230 (100)
TOTAL	318 (68.2)	79 (16.9)	69 (14.8)	466 (100)

Concerning the year of exposure beginning, 315 cases (67.5%) began exposure between 1926 and 1960, and 151 cases (32.4%) between 1961 and 1988. Looking at the percentages by year of exposure beginning, for the 1926-1960 and 1961-1988 periods, the most represented jobs were naval engineers, etc., motor mechanics, machine captains, and sailors (Table 3).

The distribution by year of incidence shows 87 cases (18.6%) incidents in the years 1993-2000, 231 (49.5%) in the period 2001-2010 and 148 (31.7%) cases in the years 2011-2018. In 2001-2010 all the jobs (except for motor mechanics, captain officer deck, machine captains, various service on ground and wireless radio operator etc.) had an incidence greater than 50% (Table 4).

4. Discussion

Our data agree with what is reported in the literature regarding the risk of mesothelioma for maritime workers regardless of the merchant marine or navy sector and the ship compartment or job performed on board [10, 14-21, 23-39]. Our cases had often worked in the Italian Navy, Merchant, or both. In each of the six specific tasks, more than 50% of the cases had certain exposure (Table 1). The most frequent jobs among our patients were 96 naval engineers etc. (20.6%), 81 motor mechanics (17.3%), 57 sailors (12.2%), and 51 (10.9%) machine captains (Table 2).

Although the earlier cancer-causing risk factors have been eliminated from newer ships, older ships with apparent work-related cancer risks, including asbestos, are still sailing as secondhand ships. Engine room crews were considered to have experienced higher asbestos exposure intensity than other crew members.

However, the distribution of cases with certain exposure among all 23 jobs (Table 2) is consistent with previously published papers [18, 20] confirming that, unlike other occupations, seamen were continually exposed to asbestos while at sea by living onboard ships and from continual release of asbestos fibers due to the motion of the vessels [10, 47].

Concerning our results about the beginning years of exposure (Table 3) was from 1926 to 1988, it must be remembered that the start of the reclamation of ships, as reported in the literature, the reduction and or elimination of asbestos use in ship construction (both merchant and naval) starting in the 1970s and during the mid-1980s [5] with various timescales in different countries. Asbestos was widely used by the Navy during World War II in shipbuilding and continued until the 1980s. In general, asbestos has been used in shipbuilding since the 1880s [48] and was prohibited in 1986 in Denmark but was used under special circumstances until 2005 [25]. Asbestos was removed from all Norwegian Naval ships in the 1980s [23-24]. The U.S. Navy ceased using asbestos-containing thermal insulation in the 1970s [8].

In general, on all ships starting from 1 January 2011, regardless of the nation whose flag the ship flies, new installation of materials that contain asbestos was prohibited according to the International Maritime Organization (IMO) that updated the International Convention for the Safety of Life at Sea

Table 2. Distribution of cases by task, job, and exposure (jobs with less than 5 cases are grouped under other jobs).

		Exposure											
		Certain			Probable			Possible			Total		
Job	Task	N	% by job	% by qualitative exposure	N	% by job	% by qualitative exposure	N	% by job	% by qualitative exposure	N	% by job	% by TOTAL JOB
Maritime Sailor	1	31	54.3	9.7	11	19.2	13.9	15	26.3	21.7	57	100	12.2
Motor Mechanics	6	67	82.7	21.06	9	11.1	11.3	5	6.1	7.2	81	100	17.3
Captains Officers Deck	1	15	57.6	4.7	5	19.2	6.3	6	23.07	8.6	26	100	5.5
Machine Captains	6	42	82.3	13.2	5	9.8	6.3	4	7.8	5.7	51	100	10.9
Naval Engineer, Stoker Charcoal Burner, Tubist	6	78	81.25	24.5	13	13.5	16.4	5	5.2	7.2	96	100	20.6
Electricians	3	21	80.7	6.6	3	11.5	3.7	2	7.6	2.8	26	100	5.5
Carpenters, Welders, Pipe Workers	3	9	64.2	2.8	4	28.5	5.06	1	7.1	1.4	14	100	3.0
Boatswain Boatman	1	7	53.8	2.2	1	7.6	1.2	5	38.4	7.2	13	100	2.7
Various Services	3	3	33.3	0.9	4	44.4	5.06	2	22.2	2.8	9	100	1.9
Kitchen Staff	4	6	50.0	1.8	4	33.3	5.06	2	16.6	2.8	12	100	2.5
Waiters	4	4	66.6	1.2	2	33.3	2.5		-		6	100	1.2
Mooring Diver Pilot Port Toolmaker	5	3	50.0	0.9	1	16.6	1.2	2	33.3	2.8	6	100	1.2
Various Services on the Ground	3	1	16.6	0.3	1	16.6	1.2	4	66.6	5.7	6	100	1.2
Steward, Quartermaster	4	4	50.0	1.2	2	25.0	2.5	2	25.0	2.8	8	100	1.7
Ship's Boy	3	6	66.6	1.8	1	11.1	1.2	2	22.2	2.8	9	100	1.9
Porter Loading Unloading Loading Unloading Officer	3	6	85.7	1.8	1	14.2	1.2		-	-	7	100	1.5
Wireless Radio, Gyroscope, Radio Telemetry, Radar	1	9	40.9	2.8	5	22.7	6.3	8	36.6	11.5	22	100	4.7
Gunner, Torpedo Gunsmith Torpedo Driver Blaster	1	5	55.5	1.5	4	44.4	5.06		-	-	9	100	1.9
Other Jobs	16	1			3			4			8	100	

Table 3. Distribution of cases by job and year of exposure beginning (jobs with less than 5 cases are grouped under other jobs).

	1926-1960			1961-1988			TOTAL	
Job	**N**	**% by job**	**% y since 1st exposure**	**N**	**% by job**	**% y since 1st exposure**	**N**	**% by job**
Maritime Sailor	38	66.6	12.06	19	33.3	12.5	57	100
Motor Mechanics	54	66.6	17.1	27	33.3	17.8	81	100
Captains Officers Deck	16	61.5	5.07	10	38.4	6.6	26	100
Machine Captains	34	66.6	10.7	17	33.3	11.2	51	100
Engineer, Stoker, Charcoal Burner, Tubist	66	68.7	20.9	30	31.2	19.8	96	100
Electricians	20	76.9	6.3	6	23.07	3.9	26	100
Carpenters Iron Welders Pipe Workers	7	50.0	2.2	7	50.0	4.6	14	100
Helmsman Boatswain Boatman	11	84.6	3.4	2	15.3	1.3	13	100
Various Services On Board	5	55.5	1.5	4	44.4	2.6	9	100
Kitchen Staff Cooks	8	66.6	2.5	4	33.3	2.6	12	100
Waiters	4	66.6	1.2	2	33.3	1.3	6	100
Mooring Diver Tugboat Pilot Port Toolmaker	5	83.3	1.5	1	16.6	0.004	6	100
Various Services On The Ground	4	66.6	1.2	2	33.3	1.3	6	100
Steward, Quartermaster	6	75.0	1.9	2	25.0	1.3	8	100
Ship's Boy	7	77.7	2.2	2	22.2	1.3	9	100
Porter Loading Unloading Loading Unloading Officer	2	28.5	0.6	5	71.4	3.3	7	100
Wireless Radio, Gyroscope, Radio, Telemetry, Radar	15	68.1	4.7	7	31.8	4.6	22	100
Gunner, Torpedo Gunsmith Torpedo Driver Blaster	8	88.8	2.5	1	11.1	0.004	9	100
Other Jobs	5	-	-	3	-	-	8	100

(SOLAS), with exceptions for those build before 2011. According to this convention, many ships still contain limited amounts of asbestos. However, "asbestos free" in one country does not necessarily mean the same in another, and so, with long global supply chains, fibers are often found. Depending on where a ship is registered, it will also have that country's standards to abide by. If a ship was built before 2002, it may contain asbestos, so the risks must be considered. A ship built between 2002 and 2011 might have the asbestos materials removed within three years. A ship built in or after 2011 might not contain asbestos. In some vessels certified as "asbestos-free", dangerous materials have been found on board due to repairs carried out in shipyards or purchases of spare parts after the issuance of such certification. Asbestos will have a significant entry path into the vessels through shipyard repairs or purchases of spare parts in countries that are not Member States of the IMO or whose national laws do not control the use of these materials [49, 50].

In Italy, the ban on the use of asbestos dates back to 1992 when the Ministerial Decree of 20 August 1999 imposed the obligation, within a year from its entry into force, to carry out the remediation or mapping and safety, of materials containing asbestos present on Italian ships built before 28 April 1994 or otherwise purchased abroad before that date (IPSEMA the Italian Institute of Insurance for the maritime sector) [51].

Table 4. Distribution of case by job and year of incidence (jobs with less than 5 cases are grouped under other jobs).

	1993-2000			2001-2010			2011-2018			TOTAL	
Job	**N**	**% by job**	**% by incidence year**	**N**	**% by job**	**% by incidence year**	**N**	**% by job**	**% by incidence year**	**N**	**% by job**
Maritime Sailor	6	10.5	6.8	33	57.8	14.2	18	31.5	12.1	57	100
Motor Mechanics	19	23.4	21.8	34	41.9	14.7	28	34.5	18.9	81	100
Captains Officers Deck	7	26.9	8.04	7	26.9	3.03	12	46.12	8.1	26	100
Machine Captains	11	21.5	12.6	21	41.1	9.09	19	37.2	12.8	51	100
Naval Engineer Naval Stoker Naval Charcoal Burner Naval Tubist	21	21.8	24.1	52	54.1	22.5	23	23.9	15.5	96	100
Electricians	4	15.3	4.5	14	53.8	6.06	8	30.7	5.4	26	100
Carpenters Iron Welders Pipe Workers	1	7.1	1.1	7	50.0	3.03	6	42.8	4.05	14	100
Helmsman Boatswain Boatman	3	23.07	3.4	7	53.8	3.03	3	23.07	2.02	13	100
Various Services On Board	1	11.1	1.1	5	55.5	2.1	3	33.2	2.02	9	100
Kitchen Staff Cooks	3	25.0	3.4	8	66.6	3.4	1	8.3	0.6	12	100
Waiters			-	4	66.6		2	33.3	1.3	6	100
Mooring Diver Tugboat Pilot Port Toolmaker			-	4	66.6	1.7	2	33.3	1.3	6	100
Various Services On The Ground	3	50.0	3.4	2	33.3	0.8	1	16.6	0.6	6	100
Steward, Quartermaster	1	12.5	1.1	4	50.0	1.7	3	37.5	2.02	8	100
Ship's Boy	1	11.1	1.1	5	55.5	2.1	3	33.3		9	100
Porter Loading Unloading Loading Unloading Officer	1	14.2	1.1	4	57.1	1.7	2	28.5	1.3	7	100
Wireless Radio Operator Gyroscope Operator Radio Operator Telemetry Operator Radar Operator	2	9.09	2.2	8	36.3	3.4	12	54.5	8.1	22	100
Gunner, Torpedo Gunsmith Torpedo Driver Blaster	3	33.3	3.4	6	66.6	2.5		-	-	9	100
Other Jobs				6			2			8	100

The data reported in the literature indicate that background airborne asbestos concentrations onboard from at least 1978 until 1992 were very low. However, many historical measurements exceeded the OSHA 8-h time-weighted average (TWA) permissible exposure limit (PEL) of 0.1 fibers/cc. Average fiber concentrations generally did not exceed historical occupational exposure limits in place. Still, measurements made during maintenance and replacement of panels or asbestos materials were excluded [2,9]. It is common for merchant seamen to make in-route repairs on asbestos-containing equipment. Airborne asbestos concentrations aboard merchant ships were found to be 51 f/cc for most short-term repair and maintenance tasks [5].

It should be remembered that the OSHA (Occupational Safety Health Administration) PELs (permissible exposure limit) values in the years 1971-1994 were gradually reduced from 12f/cc in 1971 to 0.1 f/cc in 1994 as an eight h TWA (time-weighted average). Moreover, it was demonstrated that once asbestos fibers are disturbed or released into the environment, they can continuously be re-entrained into the air in confined spaces until removed or contained [52]. This can have clear implications for the exposure of sailors in confined spaces at sea while underway, both because asbestos-containing ships are still in service and because sailors both work and live at their worksite 24 h per day, 7 days a week, and are at risk of exposure to asbestos throughout this time, making asbestos standards and permissible exposure limits (PELs) based on an 8-h workday and a 5-day work week inadequate to protect sailors' health [10].

Data on environmental measurements of asbestos published on Italian ferries [53, 54] were within the limits of the law.

Concerning the type of ship where the cases had worked, for those who have been exposed in the Navy, it was possible to reconstruct the type, the date of launch, the date of reclamation, and that of radiation; for those exposed in the merchant navy, the description of the navigation was not present in all cases (type, unit name, company name, Italian or foreign flag, type of navigation, etc.), nor it was possible to trace the information on the AMINAVI database (http://www.aminavi.cnr.it) [55-57].

It should be noted that the Navy has provided for the remediation of naval units that entered service before 1992, starting with the mapping of the presence of asbestos; as of 2020, of the 167 mapped units with permanent crew on board, including naval vessels up to port tugs, the reclamation activities involved 156 units, of which 147 units were reclaimed based on the initial reference mappings, barring the widespread elements; 9 units were initially partially reclaimed, and the completion of the activity will be carried out together with those for the remaining 11 units. The control activity and any further reclamation actions are, therefore, continuous, and any residual asbestos present is contained by encapsulation in compliance with the regulations in force on the subject, thus avoiding risks for personnel (https://www.marina.difesa.it/media-cultura/press-room/comunicati/Pagine/2020_02.aspx 09/01/2020).

However, it should be emphasized that between 1936 and 1992, 79.6% of the MM cases presented here ceased to be embarked and, therefore, exposed. Out of 85 navy ships in our case study, 11 were decommissioned after 1992, 12 were in service after 1992, 7 with complete reclamation, and 5 with partial reclamation.

Limitations of this study are in the type of data on exposure which, typical of a register, is qualitative and not quantitative data, as well as in the lack of reconstruction of the types of ships on which the cases of MM with exposure in merchant marine were embarked, dry cargo vessels, smaller ships, passenger ships, tankers and gas tankers, etc. that could be used as proxies for defining exposures to potential carcinogens. Moreover, a risk of misclassifying exposure may exist because overlap is common between different job departments or positions. In conclusion, as reported by the United States Maritime Commission, "Long after the vessel has been put to sea, flaking and cracking due to ship motions and vibrations are suspected of releasing asbestos into the surrounding space," and "In the course of a voyage it is not unusual for crewmen to repair pipes, pipe flanges, or valve leaks and this generally means a teardown situation. We must assume then that machinery and piping asbestos insulation affects not only the shipyard worker but also the crew under various conditions." [58].

Maritime work is developed internationally concerning the elements that make up the operation and manpower of the vessel. Despite this, seafarers may be under-protected with regards to ensuring their occupational health and safety while working on board because the protection of health and safety at work derived from the European Union, the International Maritime Organization, and the International Labor Organization present limitations in the application of health surveillance to seafarers [59, 60]. Ships, both as workplaces and as living spaces, have special conditions of habitability, as well as irregular environmental conditions and risk factors (such as noise, vibrations, air temperature, humidity, asbestos, and various carcinogens exposure) [61, 62]. It would be desirable for seafarers exposed in the past to be guaranteed health surveillance since many vessels built before and until at least the 80s contained asbestos materials.

Epidemiological surveillance on MMs, through the National Mesothelioma Register has allowed us to verify among cases with exclusive exposure in the maritime, navy, and merchant marine sectors that subjects with the beginning of exposure in the years 1926-1988 were all asbestos-exposed regardless of the ship's department where have provided service therefore, as already reported in the literature [37], these cases must all be considered as occupational diseases.

Institutional Review Board Statement: In Italy, malignant mesothelioma reporting to the national Registry is compulsory by law (Legislative Decree 9 April 2008, no. 81, art. 244); therefore, ethics approval is not required.

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

References

1. International Agency for Research on Cancer (IARC). IARC Monographs: Arsenic, Metals, Fibres and Dusts. Volume 100C. A Review of Human Carcinogens. 2012. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C.pdf (Last Accessed on 20 February, 2023).
2. Murbach DM, Madl AK, Unice KM, et al. Airborne concentrations of asbestos onboard maritime shipping vessels (1978-1992). *Ann Occup Hyg*. 2008;52(4):267-79. Doi: https://doi.org/10.1093/annhyg/men015
3. Hollins DM, Paustenbach DJ, Clark K, Mangold CA. A visual historical review of exposure to asbestos at puget sound naval shipyard (1962-1972). *J Toxicol Environ Health B Crit Rev*. 2009;12(2):124-56. Doi: https://doi.org/10.1080/10937400902729176 Erratum in: *J Toxicol Environ Health B Crit Rev*. 2009;12(3):224.
4. Franke K, Paustenbach D. Government and Navy knowledge regarding health hazards of asbestos: a state of the science evaluation (1900 to 1970). *Inhal Toxicol*. 2011;23 Suppl 3:1-20. Doi: https://doi.org/10.3109/08958378.2011.643417
5. Dodge DG, Beck BD. Historical state of knowledge of the health risks of asbestos posed to seamen on merchant ships. *Inhal Toxicol*. 2016;28(14):637-657. Doi: https://doi.org/10.1080/08958378.2016.1244228
6. Van De Graaff J, Poole JA. A Clinician's Guide to Occupational Exposures in the Military. *Curr Allergy Asthma Rep*. 2022;22(12):259-264. Doi: https://doi.org/10.1007/s11882-022-01051-0
7. Fleischer We, Viles Fj Jr, et al. A health survey of pipe covering operations in constructing naval vessels. *J Ind Hyg Toxicol*. 1946;28:9-16.
8. Rushworth DH. (2005) The Navy and asbestos thermal insulation. *Naval Eng J.* 35-48. Spring 2005.
9. Williams PR, Phelka AD, Paustenbach DJ. A review of historical exposures to asbestos among skilled craftsmen (1940-2006). *J Toxicol Environ Health B Crit Rev*. 2007;10(5):319-77. Doi: https://doi.org/10.1080/10937400601034191
10. Lemen RA, Landrigan PJ. Sailors and the Risk of Asbestos-Related Cancer. *Int J Environ Res Public Health*. 2021;18(16):8417. Doi: https://doi.org/10.3390/ijerph18168417
11. Jones RN, Diem JE, Ziskand MM, Rodriguez M, Weill H. Radiographic evidence of asbestos effects in American marine engineers. *J Occup Med*. 1984;26(4):281-4.
12. Velonakis EG, Tsorva A, Tzonou A, Trichopoulos D. Asbestos-related chest X-ray changes among Greek merchant marine seamen. *Am J Ind Med*. 1989;15(5):511-6. Doi: https://doi.org/10.1002/ajim.4700150504
13. Selikoff IJ, Lilis R, Levin G. Asbestotic radiological abnormalities among United States merchant marine seamen. *Br J Ind Med*. 1990;47(5):292-7. Doi: https://doi.org/10.1136/oem.47.5.292
14. Darby SC, Muirhead CR, Doll R, Kendall GM, Thakrar B. Mortality among United Kingdom servicemen who served abroad in the 1950s and 1960s. *Br J Ind Med*. 1990;47(12):793-804.Doi:https://doi.org/10.1136/oem.47.12.793
15. Varouchakis G, Velonakis EG, Amfilochiou S, Trichopoulos D. Asbestos in strange places: two case reports of mesothelioma among merchant seamen. *Am J Ind Med*. 1991;19(5):673-6. Doi: https://doi.org/10.1002/ajim.4700190511
16. Pukkala E, Saarni H. Cancer incidence among Finnish seafarers, 1967-92. *Cancer Causes Control*. 1996;7(2):231-9. Doi: https://doi.org/10.1007/BF00051299

17. 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.
18. Saarni H, Pentti J, Pukkala E. Cancer at sea: a case-control study among male Finnish seafarers. *Occup Environ Med*. 2002;59(9):613-9. Doi: https://doi.org/10.1136/oem.59.9.613
19. Hemminki K, Li X. Time trends and occupational risk factors for pleural mesothelioma in Sweden. *J Occup Environ Med*. 2003;45(4):456-61. Doi: https://doi.org/10.1097/01.jom.0000058341.05741.7e
20. Kaerlev L, Hansen J, Hansen HL, Nielsen PS. Cancer incidence among Danish seafarers: a population based cohort study. *Occup Environ Med*. 2005;62(11):761-5. https://doi.org/10.1136/oem.2005.020818
21. Forsell K, Hageberg S, Nilsson R. Lung cancer and mesothelioma among engine room crew--case reports with risk assessment of previous and ongoing exposure to carcinogens. *Int Marit Health*. 2007;58(1-4):5-13.
22. Forsell K, Eriksson H, Järvholm B, Lundh M, Andersson E, Nilsson R. Work environment and safety climate in the Swedish merchant fleet. *Int Arch Occup Environ Health*. 2017;90(2):161-168. Doi: https://doi.org/10.1007/s00420-016-1180-0
23. Ugelvig Petersen K, Lyngbeck Hansen H, Kaerlev L, Hansen J. Turning the tide: reducing mortality among Danish merchant seafarers. *Occup Environ Med*. 2020;77(11):761-768. Doi: https://doi.org/10.1136/oemed-2020-106427
24. Ugelvig Petersen K, Pukkala E, Martinsen JI, et al. Cancer incidence among seafarers and fishermen in the Nordic countries. *Scand J Work Environ Health*. 2020;46(5):461-468. Doi: https://doi.org/10.5271/sjweh.3879
25. Ugelvig Petersen K, Volk J, Kaerlev L, Lyngbeck Hansen H, Hansen J. Cancer incidence among merchant seafarers: an extended follow-up of a Danish cohort. *Occup Environ Med*. 2018;75(8):582-585. Doi: https://doi.org/10.1136/oemed-2018-105037
26. Strand LA, Martinsen JI, Koefoed VF, Sommerfelt-Pettersen J, Grimsrud TK. Asbestos-related cancers among 28,300 military servicemen in the Royal Norwegian Navy. *Am J Ind Med*. 2010;53(1):64-71. Doi: https://doi.org/10.1002/ajim.20778
27. Rafnsson V, Gunnarsdóttir H. Cancer incidence among seamen in Iceland. *Am J Ind Med*. 1995;27(2):187-93. Doi: https://doi.org/10.1002/ajim.4700270204
28. Rafnsson V, Jóhannesdóttir SG, Oddsson H, Benediktsson H, Tulinius H, Magnússon G. Mortality and cancer incidence among marine engineers and machinists in Iceland. *Scand J Work Environ Health*. 1988;14(3):197-200.Doi:https://doi.org/10.5271/sjweh.1931
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: https://doi.org/10.1080/02841860902913546
30. Roggli VL, Sharma A, Butnor KJ, Sporn T, Vollmer RT. Malignant mesothelioma and occupational exposure to asbestos: a clinicopathological correlation of 1445 cases. *Ultrastruct Pathol*. 2002;26(2):55-65. Doi: https://doi.org/10.1080/01913120252959227
31. Hemminki K, Försti A, Chen T, Hemminki A. Incidence, mortality and survival in malignant pleural mesothelioma before and after asbestos in Denmark, Finland, Norway and Sweden. *BMC Cancer*. 2021;21(1):1189. Doi: https://doi.org/10.1186/s12885-021-08913-2
32. Forsell K, Björ O, Eriksson H, Järvholm B, Nilsson R, Andersson E. Cancer incidence in a cohort of Swedish merchant seafarers between 1985 and 2011. *Int Arch Occup Environ Health*. 2022;95(5):1103-1111. Doi: https://doi.org/10.1007/s00420-021-01828-2
33. Boice JD, Cohen SS, Mumma MT, et al. Mortality among U.S. military participants at eight aboveground nuclear weapons test series. *Int J Radiat Biol*. 2022;98(4):679-700. Doi: https://doi.org/10.1080/09553002.2020.1787543
34. Till JE, Beck HL, Boice JD Jr, et al. Asbestos exposure and mesothelioma mortality among atomic veterans. *Int J Radiat Biol*. 2022;98(4):781-785. Doi: https://doi.org/10.1080/09553002.2018.1551641
35. Rapiti E, Turi E, Forastiere F, et al. A mortality cohort study of seamen in Italy. *Am J Ind Med*. 1992;21(6):863-72. Doi: https://doi.org/10.1002/ajim.4700210609
36. Giarelli L, Bianchi C, Grandi G. Malignant mesothelioma of the pleura in Trieste, Italy. *Am J Ind Med*. 1992;22(4):521-30. Doi: https://doi.org/10.1002/ajim.4700220407
37. Bianchi C, Bianchi T, Grandi G. Malignant mesothelioma of the pleura among seafarers. *Med Lav*. 2005;96(6):490-5.
38. Mensi C, Canti Z, Rivolta G, Riboldi L, Chiappino G. Il mesotelioma maligno nelle professioni marittime [Malignant mesothelioma in the maritime professions]. *Med Lav*. 2006;97(1):82.
39. Filon FL, Negro C, De Michieli P, Bovenzi M. Rischio cancerogeno da amianto nella marineria civile [Asbestos related cancers in seamen]. *G Ital Med Lav Ergon*. 2013;35(4):206-10.
40. Nesti M, Adamoli S, Ammirabile F, et al. Linee Guida per la Rilevazione e la Definizione dei casi di Mesothelioma Maligno e la Trasmissione delle Informazioni all'ISPESL da parte dei Centri Operativi Regionali; ISPESL: Roma, Italy, 2003.
41. ISTAT https://www.istat.it/it/archivio/262125 (Last Accessed on 20 February, 2023).
42. ISTAT https://www.istat.it/it/archivio/18132 (Last Accessed on 20 February, 2023).
43. DECRETO DEL PRESIDENTE DELLA REPUBBLICA 18 febbraio 1963, n. 678 Modifiche ad alcuni articoli del regolamento del Codice della navigazione, concernenti la disciplina dei titoli professionali. (GU n.136 del 24-5-1963)

44. CONTRATTO COLLETTIVO NAZIONALE DI LAVORO PER IL SETTORE PRIVATO DELL'INDUSTRIA ARMATORIALE https://www.filtcgil.it/images/Contratti/Mare/ccnl-marittimi.pdf (Last Accessed on February 20, 2023).
45. Spinazzè A, Consonni D, Borghi, et al. Asbestos Exposure in Patients with Malignant Pleural Mesothelioma included in the PRIMATE Study, Lombardy, Italy. *Int J Environ Res Public Health*. 2022;19:3390. Doi: https://doi.org/10.3390/ijerph19063390
46. Il registro nazionale dei mesoteliomi VII rapporto INAil 2021 https://www.inail.it/cs/internet/docs/alg-pubbl-il-registro-nazionale-mesoteliomi-settimo-rapporto.pdf (Last Accessed on February 20, 2023).
47. Kelman HR, Kavaler F. Mortality patterns of American merchant seamen 1973-1978. *Am J Ind Med*. 1990;17(4):423-33. Doi: https://doi.org/10.1002/ajim.4700170402
48. Harries PG. Asbestos dust concentrations in ship repairing: a practical approach to improving asbestos hygiene in naval dockyards. *Ann Occup Hyg*. 1971;14:241-54. Doi: https://doi.org/10.1093/annhyg/14.3.241
49. International Maritime Organization. Asbestos on board ships2019 10.04.2019. Available from: https://www.imo.org/en/OurWork/Safety/Pages/Asbestos.aspx (Last Accessed on 20 February, 2023).
50. International Ban Asbestos Secretariat. Why most ships still contain asbestos? Available from: http://ibasecretariat.org/jc-why-most-ships-still-contain-asbestos.php (Last Accessed on February 20, 2023).
51. https://www.gazzettaufficiale.it/eli/id/1999/10/22/099A8683/sg
52. Keyes DL, Chesson J, Hays, SM, et al. Re-entrainment of asbestos from dust in a building with acoustical plaster. Appendix 8. In Settled Asbestos Dust Sampling and Analysis; Millette, JR, Hays SM, Eds.; Lewis Publishers: Boca Raton, FL, USA, 1994.
53. Turi E, Tidei F, Paoletti L. L'esposizione all'amianto a bordo di navi: uno studio sulla situazione ambientale in due classi di navi traghetto [Asbestos exposure on board ships: a study of the environmental situation on 2 classes of ferryboats]. *Med Lav*. 1993;84(3):201-10.
54. Catasta PF, Cavalieri PG, Chiappino G, et al. Presenza di amianto sulle navi: studio sulla concentrazione di fibre aerodisperse su navi traghetto delle Ferrovie dello Stato [Presence of asbestos in naval vessels: study of airborne fiber concentrations on Italian railways ferry boats]. *Med Lav*. 2000;91(2):131-4.
55. Fiumi L, Cumbo F, Crenca C, Gallo D, Meoni C. La banca dati AMINAVI: conoscere la presenza di amianto a bordo delle navi, nel passato e nel presente [The AMINAVI database: knowing the presence of asbestos on board ships, in the past and in the present]. *Epidemiol Prev*. 2020;44(2-3):107-108. Doi: https://doi.org/10.19191/EP20.2-3.P107.028
56. http://www.aminavi.cnr.it/pages/ships.php?db=military
57. http://www.aminavi.cnr.it/pages/ships.php?db=merchant
58. Polland LD. (1979) The American merchant marine and the asbestos environment. Washington: Maritime Administration Office of Ship Construction, US Department-of Commerce, 1979:12-4.
59. Rodríguez JL, Portela RM, Pardo GM. International regulations on labour health and safety applied to fishing and maritime transport sectors. Are maritime workers under-protected. *Int Marit Health*. 2012;63(3):117-24.
60. Tozzi GA. L'approccio armonizzato alla salute e sicurezza nei porti italiani: l'esperienza del gruppo tecnico interregionale sui porti e le navi [The harmonized approach to health and safety in Italian ports: the experience of the interregional technical group on ports and ships]. *G Ital Med Lav Ergon*. 2019;41(4):299-305.
61. Vimercati L, De Maria L, Caputi A, et al. Non-Melanoma Skin Cancer in Outdoor Workers: A Study on Actinic Keratosis in Italian Navy Personnel. *Int J Environ Res Public Health*. 202030;17(7):2321. Doi: https://doi.org/10.3390/ijerph17072321
62. Geretto M, Ferrari M, De Angelis R, et al. Occupational Exposures and Environmental Health Hazards of Military Personnel. *Int J Environ Res Public Health*. 2021 18;18(10):5395. Doi: https://doi.org/10.3390/ijerph18105395

Supplementary Material

Table 1S. Maritime workers' professional qualifications by task and job.

TASK	JOB
1. Deck Crew	Cabin Boy, Deck Boy, Marine Sailor, Tankman, Deck Worker, Tractor Driver, Cabinetmaker, Shipwright Carpenter, Gun Master, Boatswain, Brass Worker, Deck Worker, Pilot, Technical Ship Inspector, Deck Officer, Captain , Accountant, Secretary, Interpreter, Bank Clerk, Guard Chief, Ticket Seller, Welder Autogenist, Inspector, Radio Operator, Telephonist, Wireless Operator, Signalman Chief, Helmsman, Bridge Crane Operator, Elevator Operator, Cashier, Cashier, Light Operator, Sentryman, Plumber, Dressing Room, Inspector, Supercargo, Auctioneer Sailor, etc.
2. Healthcare Personnel On Board	Nurse, Physician, etc.
3. Multi-Purpose Staff - Various Service Personnel	Multi-Purpose Worker, Printer, Cinematographer, Office Assistant, Stewardess, Beautician, Manicurist, Hairdresser, Barber, Gymnast, Orchestral Player, Social Entertainer, Salesman, Purser, Cabinet Maker, Carpenter, Storekeeper, etc.
4. Kitchen, Room Staff And Family	Kitchen Boy, Cook, Sub-Head Cook, Head Chef, Crew Cook, Steward, Pastry Chef, Steward, Bottler, Housekeeper, Baker, Butcher, Launderer, Ironer, Head Hors D'oeuvres, Head Pantry Steward, Head Legume, Etc Errand Boy, Footman, Commis, Cabin Steward, Lounge Steward, Porter, Head Of Quarters, Cloakroom Attendant, Butler, Nanny, Bartender, Night Watchman, Baggage Master, Cabin Boy, Etc.
5. Personnel In Charge Of Local Traffic And Coastal Fishing	Pilots, Maritime Surveyor, Mooring Men, Naval Engineering Technicians, Port Maintenance And Engineering Technicians, Divers, Divers, Boatmen, Fishing Chief, Practical, Net Fixer, Nets, Boat Master, Rower, etc.
6. Machine Crew	Brasssmith, Engineer, Refrigeration Engineer, Engine Engineer, Electrician, Mechanic, Stoker, Engineer Officer, Chief Engineer, Electrical Engineer, Autogenista Welder, Fitter, Carpenter, Tanker, Welder, Brazer, Boilermaker, Coalman, Foreman, Greaser, etc.

Table 2S. Maritime workers by jobs, task and ISTAT Professional Code.

Job	Task	ISTAT code ReNaM ISTAT Professional Code
Maritime Sailor	1	74511, 74510, 74590,
Motor Mechanics	6	74527, 62316, 623113, 623112, 62231,74520,74524, 62314, 62316
Submariners	6	31611, 74590
Captains Officers Deck	1	312610, 900015, 900019, 900030, 900039, 900069, 900076, 31261, 312610, 312611, 312617,
Machine Captains	6	312613, 312618, 31267, 312613, 312618, 31260,
Naval Engineer Naval Stoker Naval Charcoal Burner Navaltubist	6	74523, 74526, 74351, 74522,74520,74524, 732832, 863218, 74521, 62194
Electricians	3	624112, 74549,
Carpenters Iron Welders Pipe Workers	3	61234, 62142, 74545, 74540
Wood Carpenter	3	74545, 652214, 74540
Helmsman Boatswain Boatman	1	74518, 900025, 74514, 74530,
Various Services On Board	3	251613, 31215, 41298, 63411,
Kitchen Staff Cooks	4	522111, 52291, 74594,
Waiters	4	52230, 522310, 522315, 52234, 52192
Engineering Technicians, Refrigeration Engineer, Naval Plumbers Etc	1	22194, 6234
Mooring Diver Tugboat Pilot Port Toolmaker, Etc	5	62162, 74537, 312615, 74516, 74543, 6216
Various Services On The Ground	3	33433, 81110, 81298, 251613
Steward, Quartermaster	4	74594
Unqualified Personnel Cleaning	3	81410
Firefighters	3	56141
Ship's Boy	3	74517, 82214
Porter Loading Unloading Loading Unloading Officer	3	81214,
Wireless Radio Operator Gyroscope Operator Radio Operator Telemetry Perator Radar Operator	1	312414, 312421, 422411, 42245, 42249, 631918, 63198, 63198,
Gunner, Torpedo Gunsmith Torpedo Driver Blaster	1	51221, 63116

Table 3S. Navy vessels on which MM cases have been embarked according to ship's logs.

NAME	TYPE	YEAR LAUNCHED	YEAR REMEDIATION	YEAR REMOVAL	CREW
ALBENGA	TUGS FOR LOCAL AND PORT USE	1942	NO	1990	????
AIRONE	ANTI-SUBMARINE CORVETTES	1954	NO	1992	117
ALCIONE	ANTI-SUBMARINE CORVETTES	1954	NO	1992	117
ALDEBARAN	CLASS ESCORT ALERTS	1943	NO	1975	189
ALPINO	ANTI-SUBMARINE FRIGATES	1967	INCOMPLETE	2006	264
ANCONA	EXPLORER SHIP	1912	NO	1937	442
ANDREA DORIA	MISSILE CRUISERS AND HELICOPTER CARRIERS	1963	NO	1992	500
ANDROMEDA	CLASS ESCORT ALERTS	1943	NO	1971	189
APE	ANTI-SUBMARINE CORVETTES	1942	NO	1979	112
BAFILE	SHIP FOR TRANSPORTING TROOPS AND MATERIALS	1943	INCOMPLETE	1981	118
BRACCO	SUPPORT GUNNER	1944	NO	1974	1984
CADORNA	LIGHT CRUISERS	1931	NO	1951	507
CAIO DUILIO	MISSILE CRUISERS AND HELICOPTER CARRIERS	1962	NO	1990	500
CANOPO	CLASS ESCORT ALERTS	1955	NO	1984	235
CAPPELLINI	SUBMARINES	1944	NO	1977	74
CARABINIERE	ANTI-SUBMARINE FRIGATES	1971	INCOMPLETE	2008	264
CASSIOPEA	OFFSHORE MARITIME PATROL VESSELS	1988	2012	2022 in service	60
CASTORE	CLASS ESCORT ALERTS	1956	NO	1980	235
CAVEZZALE	SUPPORT SHIP DARING RAIDERS	1942	INCOMPLETE	1994	114
CENTAURO	FRIGATE	1954	NO	1984	235
GIULIO CESARE	BATTLE SHIPS	1914	NO	1948	1000
CHIMERA	ANTI-SUBMARINE CORVETTES	1943	NO	1971	112
CICLOPE	LARGER TUGS	1984	INCOMPLETE	2022 in service	??
CIGNO	CLASS ESCORT ALERTS	1955	NO	1982	235
CLIO	TORPEDO BOAT ESCORTS	1938	NO	1959	99
DUCA D'AOSTA	LIGHT CRUISERS	1934	NO	1949	578

Table 3S (*Continued*)

NAME	TYPE	YEAR LAUNCHED	YEAR REMEDIATION	YEAR REMOVAL	CREW
DUILIO	MISSILE CRUISERS AND HELICOPTER CARRIERS	10962	INCOMPLETE	1990	500
DV 408	FAST MINESWEEPERS	1945	NO	1965	24
EBANO	COASTAL NON-MAGNETIC MINESWEEPERS	1956	INCOMPLETE	1989	38
ETNA	LANDING TRANSPORT SHIP	1944	INCOMPLETE	1977	120
FAGGIO	COASTAL NON-MAGNETIC MINESWEEPERS	1952	INCOMPLETE	1980	38
FIUME	HEAVY CRUISER	1929	NO	1941	841
FLORA	ANTI-SUBMARINE CORVETTES	1942	NO	1969	112
FOLAGA	ANTI-SUBMARINE CORVETTES	1942	NO	1965	112
GAGGIA	COASTAL NON-MAGNETIC MINESWEEPERS	1955	NO	1980	38
GARIBALDI	AIRCRAFT CARRIER CRUISER	1983	1990-2022	in service	825
GAZZANA	SUBMARINES	1944	NO	1981	87
GLICINE	COASTAL MINESWEEPER	1956	NO	1980	38
GRECALE	MISSILE FRIGATES	1981	INCOMPLETE	2020	225
GRU	ANTI-SUBMARINE CORVETTES	1943	NO	1970	112
IMPAVIDO	DESTROYER	1962	NO	1991	333
IMPETUOSO	DESTROYER	1956	NO	1983	335
INDOMITO	DESTROYER	1955	NO	1983	335
INTREPIDO	DESTROYER	1962	NO	1991	333
LIBRA	OFFSHORE MARITIME PA-TROL VESSELS	1988	2012	2022 in service	60
LUIGI DI SAVOIA	MISSILE CRUISERS AND HELICOPTER CARRIERS	1936	NO	1961	640
LUPO	MISSILE FRIGATES	1976	INCOMPLETE	2004	185
MANGO	COASTAL NON-MAGNETIC MINESWEEPERS	1956	INCOMPLETE	in service	38
MARE CHIARO	GUNBOAT	1903	NO	1943	68
MAS 521	ANTI-SUBMARINE MOTORBOAT	1937	NO	1950	9
MINERVA	ANTI-SUBMARINE CORVETTES	1942	NO	1969	112
MIRTO	COASTAL NON-MAGNETIC MINESWEEPERS	1954	INCOMPLETE	2000	38

NAME	TYPE	YEAR LAUNCHED	YEAR REMEDIATION	YEAR REMOVAL	CREW
MOC	MOTO-OFFICINE COSTIERE	1943	2010	2000	26
MONTECUC-COLI	LIGHT CRUISERS	1934	NO	1964	578
NOCE	COASTAL NON-MAGNETIC MINESWEEPERS	1953	INCOMPLETE	1983	38
OLMO	COASTAL NON-MAGNETIC MINESWEEPERS	1953	INCOMPLETE	1983	38
ORIONE	OFFSHORE MARITIME PA-TROL VESSELS	2002	*"asbestos-free"*.	2022 in service	54
ORSA	MISSILE FRIGATES	1979	INCOMPLETE	2004	185
PALINURO	SAILING SCHOOL SHIP	1934	2010	2022 in service	2+72
PINO	COASTAL NON-MAGNETIC MINESWEEPERS	1953	INCOMPLETE	in service	38
PIOMARTA	SUBMARINES	1951	NO	1986	82
PLATANO	COASTAL NON-MAGNETIC MINESWEEPERS	1954	INCOMPLETE	1981	38
POMONA	ANTI-SUBMARINE CORVETTES	1942	NO	1965	112
PROTEO	SUPPORT AND RESCUE VESSELS	1951	NO	1993	118
SAETTA	GUNBOAT	1966	NO	1986	36
SAGITTARIO	MISSILE FRIGATES	1977	INCOMPLETE	2006	185
SAN GIORGIO	EX-LIGHT CRUISER DESTROYERS	1941	NO	1965-SCHOOL SHIP	360
SAN MARCO	EX-LIGHT CRUISER DESTROYERS	1941	NO	1971	360
SANDALO	COASTAL NON-MAGNETIC MINESWEEPERS	1957	INCOMPLETE	1988	38
SCIPIONE AFRIC.	LIGHT CRUISERS	1941	NO	1948	418
SIBILLA	ANTI-SUBMARINE CORVETTES	1943	NO	1975	112
STAFFETTA	OFFSHORE MARITIME PATROL VESSELS	2002	*"asbestos-free"*.	2022 in service	14
STEROPE	TEAM LOGISTICS SHIP	1944	NO	1975	??
STROMBOLI	TEAM LOGISTICS SHIP	1975	NO	2022 in service	124
VESPUCCI	SAILING SCHOOL SHIP	1931	2010	2022 in service	22+421

Table 3S (*Continued*)

NAME	TYPE	YEAR LAUNCHED	YEAR REMEDIATION	YEAR REMOVAL	CREW
VESUVIO	TEAM LOGISTICS SHIP	1943	NO	2023 in service	??
VISCHIO	COASTAL NON-MAGNETIC MINESWEEPERS	1956	INCOMPLETE	in service	38
VITTORIO VENETO	MISSILE CRUISERS AND HELICOPTER CARRIERS	1967	INCOMPLETE	2000	560
ZEFFIRO	MISSILE FRIGATES	1984	INCOMPLETE	2022 in service	225

La Medicina del Lavoro

Original article

Med Lav 2023; 114 (5): e2023042
DOI: 10.23749/mdl.v114i5.14478

Serum Specific Antibodies Do Not Seem to Have an Additional Role in the Diagnosis of Hypersensitivity Pneumonitis

Baris Demirkol[1*], Celal Satici[2], Elif Tanriverdi[2], Ramazan Eren[2], Elif Altundas Hatman[3], Hande Aytul Yardimci[4], Halide Nur Urer[5], Kursad Nuri Baydili[6], Erdogan Cetinkaya[2]

[1]University of Health Sciences Turkey, Basaksehir Cam, and Sakura City Hospital, Chest Diseases, Istanbul, Turkey
[2]University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, Chest Diseases, Istanbul, Turkey
[3]Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Occupational Medicine, Istanbul, Turkey
[4]University of Health Sciences Turkey, Basaksehir Cam and Sakura City, Department of Radiology, Istanbul, Turkey
[5]University of Health Sciences Turkey, Haseki Training and Research Hospital, Department of Pathology, Istanbul, Turkey
[6]University of Health Sciences Turkey, Hamidiye Medical Faculty, Biostatistics and Medical Informatics, Istanbul, Turkey

Keywords: Antigen; Fibrotic Hypersensitivity Pneumonitis; History of Exposure; Serum lgG Testing

Abstract

Background: *We aimed to investigate the contribution of serum immunoglobulin G testing to the history of exposure in diagnosing fibrotic hypersensitivity pneumonitis.* **Methods:** *A single-center, retrospective, cross-sectional study recruited 63 patients diagnosed with fibrotic hypersensitivity pneumonitis in line with the guidelines of the American Thoracic Society. Descriptive statistics were presented, and Kappa statistic was performed to evaluate the compatibility between the panel and the history of exposure.* **Results:** *The median age was 63 (22-81) years, and 34 (54%) were male. Forty-six patients (73%) had a positive history of exposure. Thirty-nine patients (61.9%) had a positive HP/Avian panel. The most common exposure agent was mold (34.9%), followed by parakeet (31.7%). The antibody most frequently detected was Penicillium chrysogenum lgG (36.5%), followed by Aspergillus fumigatus (31.8%). There was no compatibility between the HP/Avian panel and history of exposure (kappa coefficient=0.18, p=0.14). When exposure was only based on the history, 9 (14.3%) patients were diagnosed with fibrotic hypersensitivity pneumonitis with moderate confidence, 11 (17.5%) with high confidence, and 43 (68.3%) with definite confidence, whereas if exposure was evaluated with history and panel, 9 (14.3%) patients were diagnosed as fibrotic hypersensitivity pneumonitis with moderate confidence, 9 (14.3%) patients with high confidence and 45 (71.4%) patients with definite confidence.* **Conclusions:** *Serum-specific precipitating antibody panel does not provide additional value to the history of exposure in diagnosing fibrotic hypersensitivity pneumonitis.*

1. Introduction

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) characterized by type 3 and 4 inflammation caused by repeated inhalation of organic particles or reactive chemicals derived from fungal, bacterial, and animal proteins [1-3]. Although 11-65% of the patients with HP developed chronic fibrotic lung parenchymal abnormalities, identifying the antigen and removal from

Received 17.03.2023 – Accepted 22.08.2023
*Correponding Author: Barıs Demirkol; E-mail: barisdemirkol34@gmail.com

exposure may result in spontaneous resolution [4-8]. In line with this, identifying the antigen is crucial in patients with suspected HP.

Histopathological examination is the mainstay of the diagnosis. However, lung biopsies, including conventional transbronchial biopsy (TBB), transbronchial lung cryo-biopsy (TBLC), and surgical biopsy, may lead to complications such as hemorrhage, pneumothorax, and exacerbation of the disease [9, 10]. According to this, patients with typical radiological patterns, defined exposure to an antigen, and lymphocytosis in bronchoalveolar lavage (BAL) examinations have been diagnosed as HP without lung biopsy [10]. However, the history of exposure could not be identified in 60% of patients with HP, despite a detailed history-taking [5, 11, 12-15]. Serum-specific precipitating antibody panels, which have been used in a limited number of centers, may help clinicians to determine the antigen exposure more accurately compared to patient history [16]. There is little data on the prevalence of a positive serum immunoglobulin G (IgG) test among patients with HP, and it needs to be clarified how much evidence there is to support the use of a serum IgG test to screen for probable causal exposures [12].

Serum IgG testing against potential antigens associated with HP was suggested to identify potential exposures. Serum IgG testing was found to have high sensitivity (90%) and specificity (91%) for distinguishing individuals with HP from exposed individuals and unexposed individuals. In addition, serum IgG testing against potential antigens distinguished HP from other ILDs with a sensitivity and specificity of 83% and 68%, respectively [17]. In a recent paper published in Chest, Marinescu et al. pointed out that fibrotic HP could not easily distinguish from idiopathic pulmonary fibrosis with a physical exam, radiological findings, histopathological examination, and bronchoalveolar lavage findings. Instead, demographic features such as male gender, older age (>60 years), and smoking history may help physicians with the differential diagnosis. In addition, a history of exposure is critical for distinguishing these two clinical entities. At this point, serum IgG testing may also be important for differential diagnosis [18].

The American Thoracic Society (ATS) guideline suggested that a history of exposure or serum IgG testing should be considered for defining potentially causative anantigens12]. There is no clarity on the necessity of serum IgG testing usage among patients without a history of exposure. In line with this, to underline the importance of serum IgG testing, we aimed to investigate the contribution of serum IgG testing to the history of exposure in the diagnosis of fibrotic HP.

2. Methods

2.1 Study Design and Setting

We performed a single-center, retrospective, cross-sectional study at the Department of Pulmonology in chest diseases and thoracic surgery training and research hospital between June 2021 and June 2022. Our tertiary care center is a reference hospital in Turkey for patients with respiratory diseases, including interstitial lung diseases.

2.2 Study Population

Serum lgG testing has been routinely performed for patients with suspected HP in our clinic since January 2017. So, we evaluated 122 patients diagnosed with fibrotic HP between 2017 and 2022 who underwent serum IgG testing. Among them, 63 patients with a pathological diagnosis of fibrotic HP were included in the study. Patients treated with immunosuppressive agents, including corticosteroids before BAL analyses and serum lgG testing, and those with missing data were excluded from the study.

2.3 Data Collection

Demographic characteristics, comorbidities, presenting symptoms, physical findings, smoking history, history of antigen exposure, serum-specific precipitating antibody panel results, radiological, bronchoalveolar lavage, and pathological findings were collected from electronic medical records.

2.4 Definitions

2.4.1 History of Exposure

History of exposure was evaluated by an experienced occupational medicine physician with a work experience of 15 years in occupational health and medicine using the extrinsic factor questionnaire for ILD patients developed by Vasakova et al., which includes questions about detailed occupational history and environmental exposure [19]. A physician specialist in occupational medicine evaluated the history of antigen exposure without any knowledge about serologic tests and the diagnosis of the patients.

2.4.2 Serum IgG Testing

Immunoglobulins against specific peptide components of organic antigens could be induced after exposure and measured in peripheral blood samples. The HP/Avian panel blood samples were collected and placed in a serum-gel tube for dispatch to the laboratory, where they were studied by immunodiffusion [20]. Serum IgG testing was routinely performed only once at baseline during the initial evaluation with *Alternaria tenuis/alternate, Aspergillus fumigatus, Aureobasidium pullulans, Micropolyspora fanaei, Penicillium chrysogenum, Phoma betae, Thermoactinomyces vulgaris, Trichoderma viride*, pigeon sera, pigeon DE, cockatiel, parakeet and parrot. An HP panel result was represented as a continuous parameter and considered positive if the value was above the reference. In contrast, an avian panel result was designated as a dichotomus parameter, either positive or negative (Table 1).

Table 1. Standard HP Panel list used in Turkey.

Hypersensitivity Pneumonitis Panel	Reference range (mcg/mL)
Alternaria tenuis/ alternate	<12
Aspergillus fumigatus	<46
Aureobasidium pullulans	<18
Micropolyspora faeni	<5
Penicillium Chrysogenum	<22
Phoma Betae	<8
Thermoactinomyces vulgaris	<13
Trichoderma viride	<10
Hypersensitivity Pneumonitis Avian Panel	
Pigeon Sera	Negative/Positive
Pigeon DE	Negative/Positive
Cockatiel	Negative/Positive
Parakeet	Negative/Positive
Parrot	Negative/Positive

2.4.3 Thorax High Resolution Computes Tomography HRCT

Regarding radiologic definitions, the “typical HP” pattern suggests a diagnosis of HP. It requires a) an HRCT pattern of lung fibrosis in one of the distributions and b) at least one abnormality indicative of small airway disease. The “compatible with HP” pattern exists when the HRCT pattern and distribution of lung fibrosis varies from that of the typical HP pattern; signs of small airway disease should accompany the variant fibrosis. The ‘indeterminate for HP’ pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern [12].

2.4.4 Bronchoalveolar Lavage

BAL protocol, including the pre-procedure preparation and BAL procedure, followed the official ATS clinical practice guideline (the clinical utility of BAL cellular analysis in ILD). Accordingly, the fiberoptic bronchoscope was wedged in the orifice of a lobar or segmental bronchus of the right middle lobe or lingula division or other appropriate location based on the findings of chest images. Diagnostic BAL was done using three 50-mL sterile isotonic sodium chloride aliquots. Sequential aliquots of normal saline of at least 100 mL (no more than 300 mL) should be instilled, and at least 30% returned for optimal sampling [21]. Cellular analysis in BAL fluid was evaluated according to ATS guidelines [12].

2.4.5 Biopsy Technique

Three or more biopsies were obtained from the involved lung parenchyma according to the HRCT scan appearance in the TBLC procedure, which was performed as recommended [22]. TBB was performed in patients unsuitable for general anesthesia, and video-assisted thoracic surgery was performed upon the council's decision for patients who could not be diagnosed with TBB or TBLC.

2.4.6 Pathological Diagnosis

Regarding pathological definitions, the typical HP characteristics on histology were lymphocyte predominance, chronic bronchiolocentric inflammation, poorly formed non-necrotizing granulomas, giant cells, airway-centered interstitial fibrosis, and an alternative diagnosis. The probable HP pattern that differs from the typical HP pattern is the lack of poorly formed non-necrotizing granulomas. The indeterminate HP characteristics on histology were defined as selected idiopathic interstitial pneumonia patterns (cellular NSIP, organizing pneumonia, or peribronchiolar metaplasia without other features to suggest fibrotic HP) or cellular interstitial pneumonia/cellular bronchiolitis and absence of alternative diagnosis [12].

Patients were diagnosed with fibrotic HP utilizing the appropriate combination of antigen exposure, BAL results, and radiological and pathological criteria by a multidisciplinary discussion (MDD) comprising a pulmonologist, a chest surgeon, an occupational medicine physician, a rheumatologist, a radiologist, and a pathologist, in line with the ATS guidelines [12].

2.5 Data Analysis and Statistical Methods

Descriptive statistics were performed using IBM SPSS Statistics 25. Categorical variables were presented as proportions and counts. Continuous data were presented as mean and standard deviation if normally distributed, and median and interquartile range were used if not normally distributed. Kappa statistic was performed to evaluate the compatibility between the panel and the history of exposure. A p-value <0.05 was considered statistically significant.

3. Results

A total of 63 patients with fibrotic HP were included in the study. Thirty-four (54%) patients were female, and the median age was 63 years (22-81). Thirty-six (57.1%) patients were never smokers, and 35 (55.6%) had at least one comorbidity. The most common comorbidity was diabetes mellitus, hypertension, asthma, ischemic heart diseases, cardiac failure, and gastroesophageal reflux. The mean forced expiratory volume in the first second (FEV_1) (%) was 72.9±22.5, the mean forced vital capacity (FVC) (%) was 67.66±20.94, and the mean diffusing capacity for carbon monoxide (DLCO) (%) was 47.92±15.34. Fifty-one (80,9%) of 63 patients had BAL. Among them, the lymphocyte count was greater than 15% in BAL analyses of 37 patients. All patients underwent an invasive lung biopsy. Of these, 4 (6.4%) were diagnosed with TBB, 15 (23.8%) with TBLC, and 44 (69.8%) with a surgical biopsy (Table 2).

Regarding the history of exposure, forty-six patients (73%) had a positive history of exposure. The most common exposure agent was mold (34.9%), followed by parakeet (31.7%) and pigeon (17.5%). Thirty-nine patients (61.9%) had a positive HP/Avian panel. The antibody detected the most was *Penicillium chrysogenum* IgG (36.5%), followed by *Aspergillus fumigatus* (31.8%) and *Phoma betae* (22.2%). Regarding radiological findings, 24 (38.1%) patients had a typical pattern, 31 (49.2%) had a compatible pattern, and 8 (12.7%) had an indeterminate pattern. In comparison, 37 (58.7%) patients were diagnosed as typical for HP, 20 (31.7%) patients were diagnosed as probable HP, and 6 (9.5%) were diagnosed as indeterminate for HP with pathological evaluation (Table 3). Among six patients with indeterminate histopathology, one had a typical radiological pattern, and five had compatible radiological patterns in thorax HRCT. Three of these patients had a positive serological test, and three had a positive history of exposure. Regarding bronchoalveolar lavage findings, lymphocytosis was reported in all these patients. After MDD, these six patients were diagnosed with fibrotic HP.

There was no compatibility between the HP/Avian panel and history of exposure (kappa coefficient=0.18, p=0.14). If the exposure was only assessed based on the history, 9 (14.3%) patients were diagnosed as HP with moderate confidence, 11 (17.5%) patients were diagnosed with high confidence, and 43 (68.3%) patients were diagnosed with definite confidence, whereas 9 (14.3%) patients were

Table 2. Demographic, clinical characteristics, and laboratory findings of patients with fibrotic hypersensitivity pneumonitis.

PARAMETERS	ALL PATIENTS, n(%)
Age (years), median (min-max)	63 (22-81)
Female gender, n(%)	34(54)
Comorbidities, n(%)	
Any comorbidity	35(55.6)
Diabetes mellitus	14(22.2)
Hypertension	13(20.6)
Asthma	5(7.9)
Ischemic heart diseases	5(7.9)
Cardiac failure	2(3.2)
Gastroesophageal reflux	2(3.2)
Smoking Status, n(%)	
Never smoker	36(57.1)
Ever smoker	21(33.3)
Active smoker	6(9.6)
Smoking (pack/year), median (min-max)	0(0-75)
Pulmonary function test, mean±SD/median (min-max)	
FEV_1(lt)	1.94±0.74
FEV_1 (%)	72.9±22.5
FVC(lt)	2.16(0.82-5.26)
FVC(%)	67.66±20.94
FEV_1/FVC(%)	85.1(59-123)
DLCO(ml/min/mmHg)	3.7(1.3-21)
DLCO(%)	47.92±15.34
Six minutes walking test(meter), mean± SD	382.1±100.2
< 40 years of age	435.7±98
40 - 59 years of age	368.7±107.3
≥ 60 years of age	376.2±96.8
Bronchoalveolar lavage findings, mean±SD/median (min-max)	
Total cell count (cells/mm^3)	390(120-1520)
Lymphocyte count (%)	20(5-75)
Neutrophil count (%)	26.38±13.24
Diagnostic technique, n(%)	
Transbronchial biopsy	4(6.4)
Transbronchial lung cryobiopsy	15(23.8)
Surgical biopsy	44(69.8)

Abbreviations: FEV_1*: forced expiratory volume in the first second, FVC: forced vital capacity, DLCO: diffusing capacity for carbon monoxide.*

Table 3. Exposure evaluation with history and panel, radiological and pathological findings of patients with hypersensitivity pneumonitis.

History of exposure (+), n(%)	**46(73)**
History of exposure regarding HP panel, n(%)	24(38.1)
Mold exposure	22(34.9)
Farmer	8(12.7)
History of exposure regarding Avian panel, n(%)	33(52.4)
Parakeet	20(31.7)
Pigeon	11(17.5)
Cockatiel	3(4.8)
Parrot	2(3.2)
HP/Avian panel (+), n(%)	39(61.9)
HP panel (+)	33(52.4)
Alternia tenuis/alternata IgG	1(1.6)
Aspergillus fumigatus lgG	20(31.8)
Aureobasidium pullulans lgG	3(4.8)
Microplyspora faeni lgG	8(12.7)
Pencillum Chrysogenum lgG	23(36.5)
Phoma betae IgG	14(22.2)
Thermoactinomyces vulgaris lgG	8(12.7)
Trichoderma viride lgG	7(11.1)
Avian panel (+)	15(23.8)
Pigeon Sera	3(4.8)
Pigeon DE	7(11.1)
Cockatiel	7(11.1)
Parakeet	11(17.5)
Parrot	4(6.4)
Radiological diagnosis, n(%)	
Indeterminate for HP	8(12.7)
Compatible with HP	31(49.2)
Typical HP	24(38.1)
Pathological diagnosis, n(%)	
Indeterminate for HP	6(9.5%)
Probable HP	20(31.7%)
Typical HP	37(58.7%)

diagnosed with moderate confidence, 9 (14.3%) patients were diagnosed with high confidence and 45 (71.4%) patients were diagnosed with definite confidence if the exposure was evaluated with history or panel (Table 4).

Detailed evaluation of the diagnosis of patients with fibrotic HP based on the incorporation of imaging, exposure assessment, BAL lymphocytosis, and histopathological findings were depicted in Figure 1A and Figure 1B.

4. Discussion

The serum-specific precipitating antibody test is recommended for diagnosing HP in current guidelines, albeit with shallow evidence. However, serum-specific antibody panel does not seem to contribute to the diagnosis of fibrotic HP based on the results of this study.

A study conducted on 108 patients with suspected fibrosing ILD assessed the accuracy of serum antigen-specific IgG test based on history of exposure or multidisciplinary diagnosis, in addition to HRCT imaging. Independent of serum-specific antibodies, HRCT findings, history of exposure, and an interdisciplinary approach helped to diagnose 89% of the patients. While 60% of patients with positive antibodies reported no exposure, 32% of patients with negative antibody results had a history of exposure. The results of this study suggested that serum-specific antibodies could not have an important role in the diagnosis of fibrotic HP [23]. In our research, 47 (73%) of all patients evaluated by an occupational medicine physician had a history of exposure. While the panel was negative in 32.6% of the patients with a history of exposure, 47.1% of the patients with a positive panel had no history of exposure. No compatibility was found between the panel and the history of exposure (kappa coefficient=0.18, p=0.14).

In patients for whom culprit antigen cannot be identified by detailed history-taking, there is data that we can capture with serum IgG testing, so this panel has begun to be used routinely by guidelines [12]. In addition, since the same patient may have more than one antigen, the idea that a history

Table 4. Compatibility between HP/Avian panel and the history of exposure and diagnostic level of confidence combined with exposure, radiological and pathological findings.

	HP Panel		kappa coefficient	p-value
History of exposure	**(-)**	**(+)**		
(-)	22(56,4)	17(43,6)	0.180	0.140
(+)	8(33.3)	16(66.7)		
Diagnostic level of confidence combined with exposure, radiological and pathological findings				
All Patients		***n(%)***		
Exposure evaluated with only history				
Moderate confidence		9(14.3)		
High confidence		11(17.5)		
Definite confidence		43(68.3)		
Exposure evaluated with history or panel				
Moderate confidence		9(14.3)		
High confidence		9(14.3)		
Definite confidence		45(71.4)		

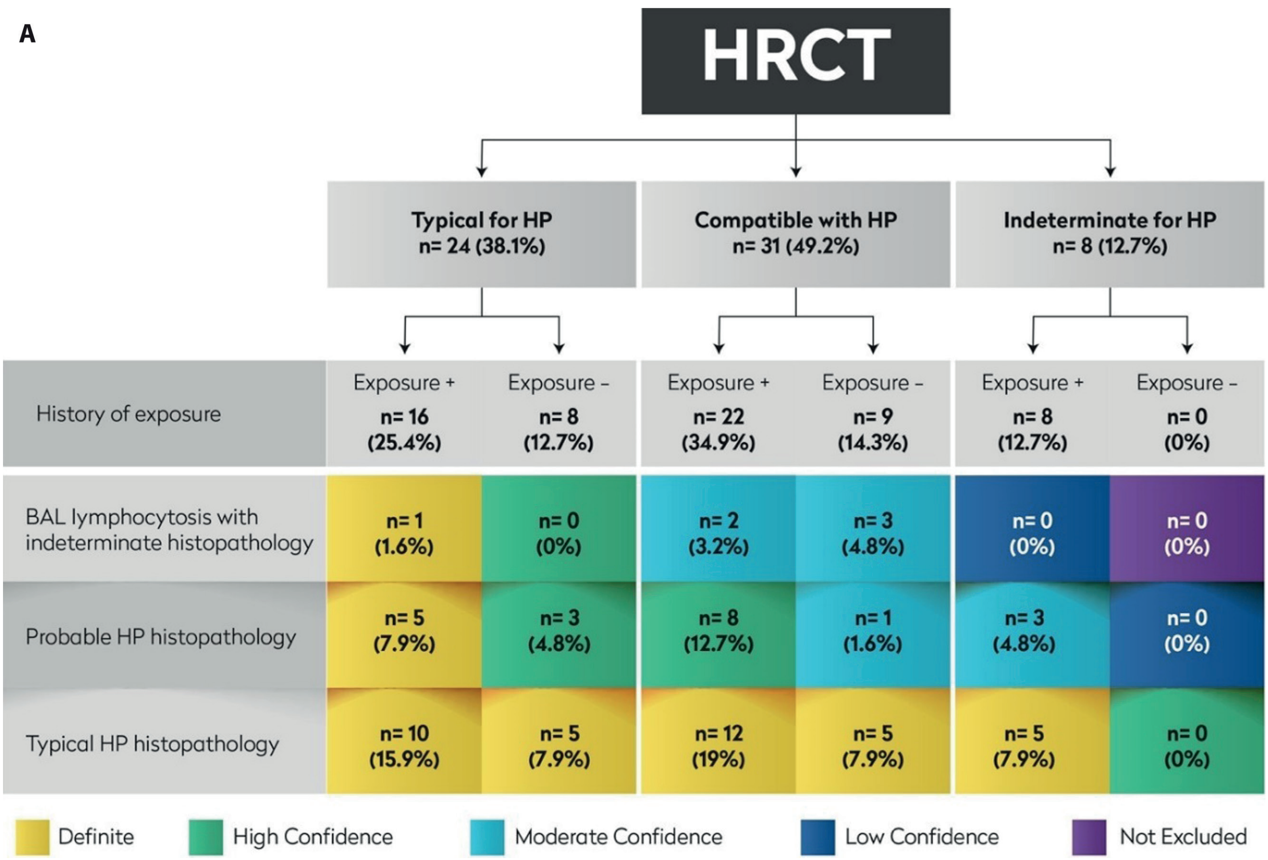


Figure 1A. Detailed evaluation of diagnosis of patients with FHP based on the incorporation of imaging, history of exposure, BAL lymphocytosis and histopathological findings.

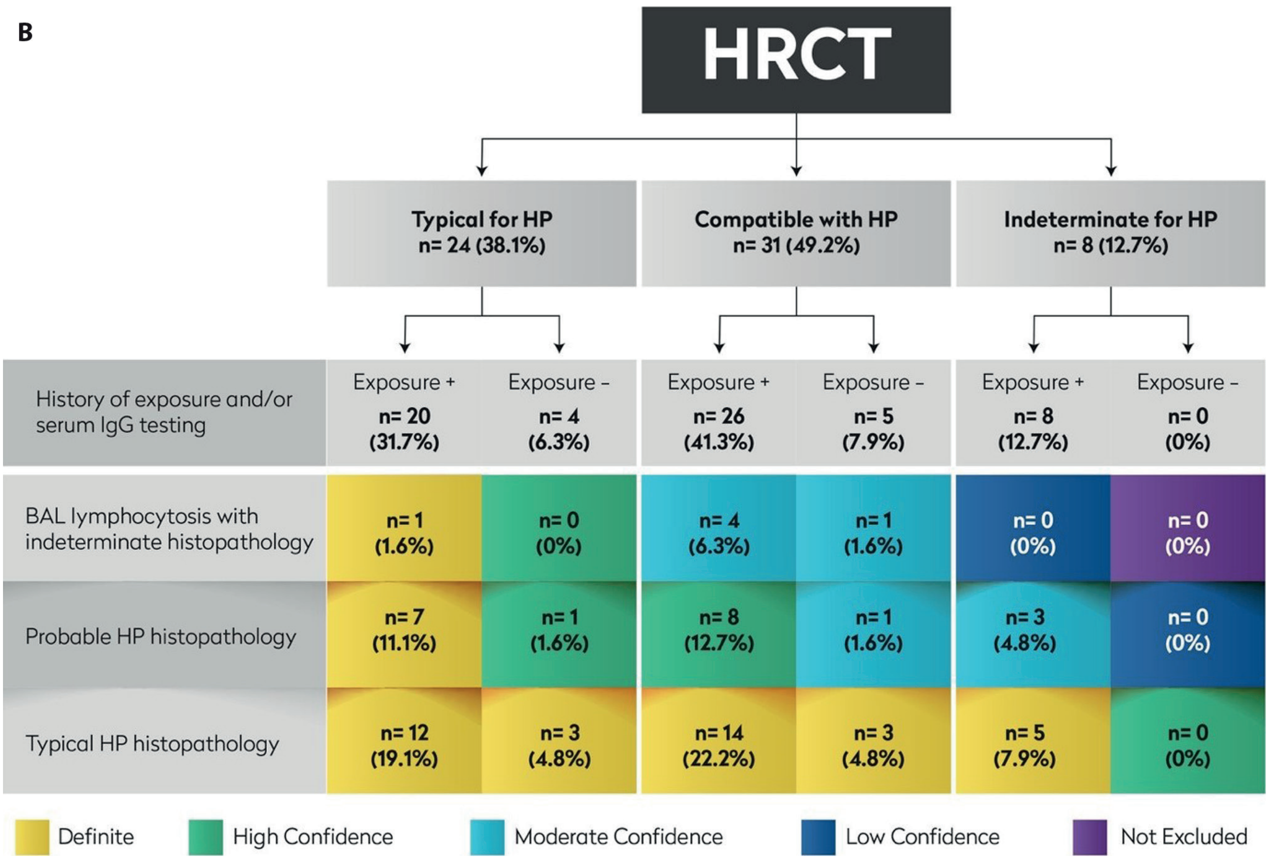


Figure 1B. Detailed evaluation of diagnosis of patients with FHP based on the incorporation of imaging, history of exposure and/or serum IgG testing, BAL lymphocytosis and histopathological findings.

of environmental exposure may be insufficient to detect a culprit antigen suggests that serum IgG testing may be advantageous [24]. However, data on the use of serum IgG are contradictory in the literature, and their sensitivity-specificity ranges are wide. The sensitivity of serum antigen-specific antibody testing in CHEST guidelines ranged from 25% to 96% and specificity from 60% to 100% [25]. One of the possible reasons for the conflicting data is the detection of antigen positivity in healthy people. Positive precipitins were found in 40-60% of exposed healthy patients, indicating the immunization state [26-28]. Another study comparing ILD and HP patients reported positive serum lgG in 7% of non-HP patients [29]. The findings of our study suggest that a detailed antigen exposure history taken by the occupational medicine physician may be sufficient for diagnosing pneumonia, with or without a serum IgG test.

Another reason for the contradictory results of serum IgG tests is that these panels need to be customized for individuals and regions. Notably, a study stating that serum IgG test may benefit clinical practice was conducted for antigens specific to an area with a high prevalence of farmer's lung [16]. Another study stated that antibody tests would contribute more to the diagnosis after being personalized depending upon the characteristics particular to the region, and an exemplary panel may include molds, bacteria, animal proteins, and chemicals [24]. Our study was strong in that respect; although Turkey does not have a personalized test, the agents detected the most in the history of exposure were also included in the serum IgG testing. However, since the most common agents were mold and bird in patients with a history of exposure, the standard test we used may be suitable for our region. On the other hand, the algorithm leading to diagnosis by evaluating the history and the panel together did not significantly contribute to the algorithm leading to diagnosis by history alone.

Except for the exposures in the patient's history, the fact that the antigens he had never been exposed to until that day were positive in the panel was considered cross-reactivity positivity [30]. As stated earlier in our study, the antigens thought to be not the subject of exposure were positive in the panel, suggesting that they may correspond with cross-reactivity because the antigens in the standard panel were handled by an occupational medicine physician with a detailed history-taking for each patient.

There is also the presence of antigens that are not commercially available or produced in the panels, although they were detected during history-taking. Rognon et al. found *Lichtheimia corymbifera* antigen in a farmer's lung, and their study, which would be a preliminary step for kit development, was presented [31]. In Barrera's study, Saccharopolyspora rectivirgula antigen was defined as another cause of Farmer's Lung [32]. These studies show the presence of missing antigens in the standardized HP panel, which we also used, and suggest that its diagnostic value may be limited.

Another limitation of the serum lgG test is the lack of standardized antigen preparations, immunoassay techniques, and variable diagnostic thresholds for quantitative lgG tests. Nevertheless, there is a lack of data to consistently support the test as a reproducible and accurate diagnostic tool [25]. These non-standardized tests have been evaluated in various studies, and the ELISA test is thought to be more valuable [17]. In our research, the ELISA test and serum IgG test were used.

Serum lgG testing has been thought to be more significant in non-fibrotic HP studies [33-35]. Salisbury et al. did not recommend using antibody tests to diagnose fibrotic HP because antibody positivity may exist in healthy people but have a history of exposure, or antibody tests cannot detect each antigen in patients with a high diversity of antigens [36]. Our study's low serum IgG test results may be associated with the fibrotic HP diagnosis of our patients.

In the majority of these studies, the history of exposure was questioned by pulmonologists. Moreover, the decision was not taken from the diagnosis of the patients together with histopathological findings [25, 37]. Our research benefits from the comprehensive investigation with the addition of an occupational medicine physician to the MDD team [38]. The detailed evaluation of the patients, including a clear history of exposure taken by an occupational medicine physician, the pathological diagnosis of all patients, and the diagnostic decisions made in our MDD strengthen our study. Our study was limited by its retrospective nature, and it was a single-center study. As pointed out above, panels of serum IgG tests do not include all antigens. Patients may not remember especially a remote history of exposure, which can lead to a recall bias. Since only an occupational medicine physician had a history of exposure with a validated questionnaire, we could not present the possible differences between the classical history of exposure taken by clinicians and the history of exposure with a validated questionnaire taken by an occupational medicine physician.

5. Conclusions

A detailed history of antigen exposure taken by an occupational physician, and the multidisciplinary approach, improve clinicians' decisions in diagnosing patients with hypersensitivity pneumonitis with or without serum IgG testing. Considering that serum IgG tests are not easily accessible, it's thought that a detailed history-taking still maintains its place in diagnosis.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Local Institutional Ethics Committee (ethics approval number: 2006).

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

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

References

1. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med*. 2012;186(4):314-324. Doi: 10.1164/rccm.201203-0513CI
2. Basis of Disease. Kumar V, Abbas AK, Fausto N, Aster JC, eds. Robbins and Cotran Pathologic. 8th ed. Philadelphia, Pa: Saunders; 2010.
3. Adkinson NF. Hypersensitivity Pneumonitis. Middleton's Allergy: Principles and Practice. 8th Ed. Saunders; 2013.
4. Hanak V, Golbin JM, Hartman TE, Ryu JH. High-resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. *Chest*. 2008;134(1):133-138. Doi: 10.1378/chest.07-3005
5. Fernández Pérez ER, Swigris JJ, Forssén AV, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest*. 2013;144(5):1644-1651. Doi: 10.1378/chest.12-2685
6. Mooney JJ, Elicker BM, Urbania TH, et al. Radiographic fibrosis score predicts survival in hypersensitivity pneumonitis. *Chest*. 2013;144(2):586-592. Doi: 10.1378/chest.12-2623
7. Johannson KA, Elicker BM, Vittinghoff E, et al. A diagnostic model for chronic hypersensitivity pneumonitis. *Thorax*. 2016;71(10):951-954. Doi: 10.1136/thoraxjnl-2016-208286
8. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of Hypersensitivity Pneumonitis among an Insured Population in the United States: A Claims-based Cohort Analysis. *Ann Am Thorac Soc*. 2018;15(4):460-469. Doi: 10.1513/AnnalsATS.201704-288OC
9. Bando M, Ohno S, Hosono T, et al. Risk of Acute Exacerbation After Video-assisted Thoracoscopic Lung Biopsy for Interstitial Lung Disease. *J Bronchology Interv Pulmonol*. 2009;16(4):229-235. Doi: 10.1097/LBR.0b013e3181b767cc
10. Troy LK, Grainge C, Corte TJ, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med*. 2020;8(2):171-181. Doi: 10.1016/S2213-2600(19)30342-X
11. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc*. 2007;82(7):812-816. Doi: 10.4065/82.7.812
12. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline [published correction appears in *Am J Respir Crit Care Med*. 2021 Jan 1;203(1):150-151] [published correction appears in *Am J Respir Crit Care Med*. 2022 Aug 15;206(4):518]. *Am J Respir Crit Care Med*. 2020;202(3):e36-e69. Doi: 10.1164/rccm.202005-2032ST
13. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity Pneumonitis: Perspectives in Diagnosis and Management. *Am J Respir Crit Care Med*. 2017;196(6):680-689. Doi: 10.1164/rccm.201611-2201PP
14. Salisbury ML, Gross BH, Chughtai A, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. *Eur Respir J*. 2018;52(2):1800443. Published 2018 Aug 16. Doi: 10.1183/13993003.00443-2018
15. Morell F, Villar A, Montero MÁ, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med*. 2013;1(9):685-694. Doi: 10.1016/S2213-2600(13)70191-7
16. Fenoglio CM, Reboux G, Sudre B, et al. Diagnostic value of serum precipitins to mould antigens in active hypersensitivity pneumonitis. *Eur Respir J*. 2007;29(4):706-712. Doi: 10.1183/09031936.00001006
17. Jenkins AR, Chua A, Chami H, et al. Questionnaires or Serum Immunoglobulin G Testing in the Diagnosis of Hypersensitivity Pneumonitis among Patients with Interstitial Lung Disease. *Ann Am Thorac Soc*. 2021;18(1):130-147. Doi: 10.1513/AnnalsATS.202005-419OC
18. Marinescu DC, Raghu G, Remy-Jardin M, et al. Integration and Application of Clinical Practice Guidelines for the Diagnosis of Idiopathic Pulmonary Fibrosis and Fibrotic Hypersensitivity Pneumonitis. *Chest*. 2022;162(3):614-629. Doi: 10.1016/j.chest.2022.06.013
19. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity Pneumonitis: Perspectives in Diagnosis and Management. *Am J Respir Crit Care Med*. 2017;196(6):680-689. Doi: 10.1164/rccm.201611-2201PP
20. Hypersensitivity Pneumonitis FEIA Panel II, Mayo Clinic Laboratories; Hypersensitivity Pneumonitis Panel, Test Code: Y165, Viracor Eurofins.
21. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*. 2012;185(9):1004-1014. Doi: 10.1164/rccm.201202-0320ST
22. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease: Retrospective Analysis of 74 Cases. *Chest*. 2017;151(2):400-408. Doi: 10.1016/j.chest.2016.09.002
23. Giacomi F, Andreano A, Faverio P, et al. Utility of precipitating antibody testing in the diagnostic evaluation of chronic hypersensitivity pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis*. 2017;34(2):149-155. Doi: 10.36141/svdld.v34i2.5467

24. Nogueira R, Melo N, Novais E Bastos H, et al. Hypersensitivity pneumonitis: Antigen diversity and disease implications. *Pulmonology*. 2019;25(2):97-108. Doi: 10.1016/j.pulmoe.2018.07.003
25. Fernández Pérez ER, Travis WD, Lynch DA, et al. Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. *Chest*. 2021;160(2):e97-e156. Doi: 10.1016/j.chest.2021.03.066
26. Morell F, Villar A, Ojanguren I, Muñoz X, Cruz MJ. Hypersensitivity Pneumonitis: Challenges in Diagnosis and Management, Avoiding Surgical Lung Biopsy. *Semin Respir Crit Care Med*. 2016;37(3):395-405. Doi: 10.1055/s-0036-1580692
27. Morisset J, Johannson KA, Jones KD, et al. Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis: An International Modified Delphi Survey. *Am J Respir Crit Care Med*. 2018;197(8): 1036-1044. Doi: 10.1164/rccm.201710-1986OC
28. Jędrych ME, Szturmowicz M, Bestry I, Kuś J. Alergiczne zapalenie pęcherzyków płucnych – kryteria rozpoznania, leczenie, rokowanie i zapobieganie [Hypersensitivity pneumonitis: Diagnostic criteria, treatment, prognosis and prevention]. *Med Pr*. 2016;67(4):517-527. Doi: 10.13075/mp.5893.00406
29. Szturmowicz M, Garczewska B, Jędrych ME, et al. The value of serum precipitins against specific antigens in patients diagnosed with hypersensitivity pneumonitis - retrospective study. *Cent Eur J Immunol*. 2019;44(4): 390-394. Doi: 10.5114/ceji.2019.92791
30. Millon L, Rognon B, Valot B, et al. Common peptide epitopes induce cross-reactivity in hypersensitivity pneumonitis serodiagnosis. *J Allergy Clin Immunol*. 2016;138(6):1738-1741.e6. Doi: 10.1016/j.jaci.2016.06.037
31. Rognon B, Barrera C, Monod M, et al. Identification of Antigenic Proteins from Lichtheimia corymbifera for Farmer's Lung Disease Diagnosis. *PLoS One*. 2016;11(8):e0160888. Published 2016 Aug 4. Doi: 10.1371/journal.pone.0160888
32. Barrera C, Millon L, Rognon B, et al. Immunoreactive proteins of Saccharopolyspora rectivirgula for farmer's lung serodiagnosis. *Proteomics Clin Appl*. 2014; 8(11-12):971-981. Doi: 10.1002/prca.201400024
33. De Sadeleer LJ, Hermans F, De Dycker E, et al. Effects of Corticosteroid Treatment and Antigen Avoidance in a Large Hypersensitivity Pneumonitis Cohort: A Single-Centre Cohort Study. *J Clin Med*. 2018;8(1):14. Published 2018 Dec 21. Doi: 10.3390/jcm8010014
34. Ojanguren I, Morell F, Ramón MA, et al. Long-term outcomes in chronic hypersensitivity pneumonitis. *Allergy*. 2019;74(5):944-952. Doi: 10.1111/all.13692
35. Wang LJ, Cai HR, Xiao YL, Wang Y, Cao MS. Clinical characteristics and outcomes of hypersensitivity pneumonitis: a population-based study in China [published correction appears in Chin Med J (Engl). 2021 Jan 11;134(3):378]. *Chin Med J (Engl)*. 2019;132(11): 1283-1292. Doi: 10.1097/CM9.0000000000000256
36. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. *Am J Respir Crit Care Med*. 2017;196(6):690-699. Doi: 10.1164/rccm.201608-1675PP
37. Yang SR, Beasley MB, Churg A, et al. Diagnosis of Hypersensitivity Pneumonitis: Review and Summary of American College of Chest Physicians Statement. *Am J Surg Pathol*. 2022;46(4):e71-e93. Doi: 10.1097/PAS.0000000000001827
38. Lee CT, Adegunsoye A, Chung JH, et al. Characteristics and Prevalence of Domestic and Occupational Inhalational Exposures Across Interstitial Lung Diseases. *Chest*. 2021;160(1):209-218. Doi: 10.1016/j.chest.2021.02.026

La Medicina del Lavoro

Original article

Med Lav 2023; 114 (5): e2023044
DOI: 10.23749/mdl.v114i5.14973

Recognized Occupational Diseases in Italy's Friuli-Venezia Giulia and Liguria Regions (2010-2021)

Francesca Larese Filon[1], Jessica Granzotto[1], Antonio Bignotto[1], Barbara Alessandrini[2], Paolo Barbina[3], Francesca Rui[1]

[1]Unit of Occupational Medicine, Post graduated School in Occupational Medicine University of Trieste, Italy
[2]Direzione Centrale Salute - Regione Friuli Venezia Giulia
[3]Centro Regionale Unico per l'Amianto - Azienda Sanitaria Universitaria Giulino Isontina, Monfalcone, Italy

Keywords: Occupational Diseases; Incidence Rate Ratios; Italy; Time Trend

Abstract

Background: *The study of recognized occupational diseases trend is important to understand the preventive approach needed in the future, however, while numbers of occupational diseases are available on web, data on incidence are missing. The aim of our study was to analyze the trend and the incidence rate ratio (IRR) of recognized occupational diseases in Italy, in Friuli-Venezia Giulia region (FVG) and Liguria region from 2010 to 2021.* **Methods:** *Numbers of recognized occupational diseases by the Italian National Insurance for Occupational Diseases (INAIL) were analyzed and incidence were calculated considered the total number of workforces in the area. A Poisson regression model was used to estimate incidence trends.* **Results:** *FVG region presented a higher incidence of all occupational diseases compared to Italy and to Liguria in the period considered. The overall incidence in 2019 was 175, 91.8 and 108 cases for 100,000 workers, for FVG, Liguria and Italy respectively. Musculoskeletal disorders (MSDs) were the majority of occupational diseases with 100, 51 and 82.8 cases per 100,000 workers, in FVG, Liguria and Italy, respectively. Incidence of occupational cancers was 16, 10 and 4.9 cases per 100,000 workers, in FVG, Liguria and Italy, respectively. The annual change of incidence from 2010 to 2019 was positive for MSDs (IRR 1.06; 95%CI 1.06 to 1.07) and decreasing for the other causes in Italy. In FVG region the trend was positive for MSDs (IRR 1.05; 95%CI 1.04 to 1.06), for respiratory diseases (IRR 1.03; 95%CI 1.00 to 1.05) and pleural plaques (IRR 1.03; 95%CI 1.00 to 1.06). In Liguria the trend was positive for MSDs (IRR 1.17; 95%CI 1.15-1.19) and for pleural plaques (IRR 1.07; 95%CI 1.03-1.12). Stable trends were found for cancers. Declining trend was shown for noise induced hearing loss and skin diseases.* **Conclusions:** *FVG region presented a higher incidence of recognized occupational diseases compared to Liguria region and Italian data. Results that can be explained by a higher propensity of claiming for occupational diseases in workers, mainly for MSDs disorders. For cancers and asbestos-related diseases the higher incidence can be attributable to high exposure to asbestos in FVG and Liguria workers mainly in shipyard and dock activities.*

1. Introduction

The study of occupational diseases trend is needed to better define the preventive strategies to be applied to contrast or at least limit the onset of these diseases. Trend in incidence data, reporting number of occupational diseases in relationship with workforce are limited in scientific literature.

Stocks et al. [1] studied noise-induced hearing loss, carpal tunnel syndrome, upper limb

Received 02.07.2023 – Accepted 06.09.2023
*Corresponding Author: Francesca Larese Filon; E-mail: larese@units.it

musculoskeletal disorders, contact dermatitis and asthma in ten EU countries from 2000 to 2012 finding a general decrease in ODs with few exceptions. Noise-induced hearing loss was reported to increase only in some EU Countries (Belgium, Spain, Switzerland and the Netherlands). Trends in carpal tunnel syndrome and upper limb musculoskeletal disorders are completely different in different EU Countries, mainly due to different reporting and recognizing systems [1]. EUROSTAT [2] reported data from some EU Countries on ODs showing wide differences due to the reporting classification system.

The lack of precise data on ODs and the under-reporting phenomenon in official data determined the set-up of voluntary reporting schemes such as The Health and Occupational Reporting (THOR) Network in the UK; also, for that system, the under-reporting was recently studied by Gittins et al. [3] to suggest a statistical analysis to unjust for "zero" responders.

In Italy, van der Molen et al. [4] found, in agriculture, a significant increase in claims for musculoskeletal disorders (MSDs) from 2008, mainly due to a changeover of recognizing system applied by the Italian Insurance against occupational diseases (INAIL - Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro). Recently Larese Filon et al. [5] performed the same analysis in industrial and services sectors from 2006 to 2019, finding a lower incidence of occupational diseases but with a similar increasing trend for MSDs and a decreasing trend for ear diseases.

To better analyze ODs in Italy, there is the need to evaluate recognized ODs and compare Italian to Regional data: local exposures and reporting attitudes can influence the difference in incidence of ODs that are interesting to discuss.

This study analyzed the incidence and trend of recognized ODs in Italy compared to the Friuli-Venezia Giulia and Liguria regions. We chose these two regions because both have a similar number of workers and are characterized by high past exposure to asbestos in shipyard and dock sectors [6, 7].

2. Methods

2.1. Study Design and Procedures

ODs recognized by national insurance INAIL in Italy, Friuli-Venezia Giulia, and Liguria regions in all sectors from 2010 to 2021 were considered. Incidence of ODs was determined for all diseases and for six groups of diseases present in the Italian list: Cancers (C00-D48); mesothelioma (C45); asbestosis (J61); pleural plaques (J92); noise induced hearing loss (H83.3); musculoskeletal and connective tissue diseases (M00-M99); respiratory diseases (J00-J99); skin diseases (L00-L99). The number of recognized ODs for industrial and services sectors was taken from the INAIL website available for FVG region (Flussi Informativi INAIL - Regioni) [8].

The number of total workers in the Industrial and services sectors was taken from a database provided by the Italian National Institute of Statistics (ISTAT) [9].

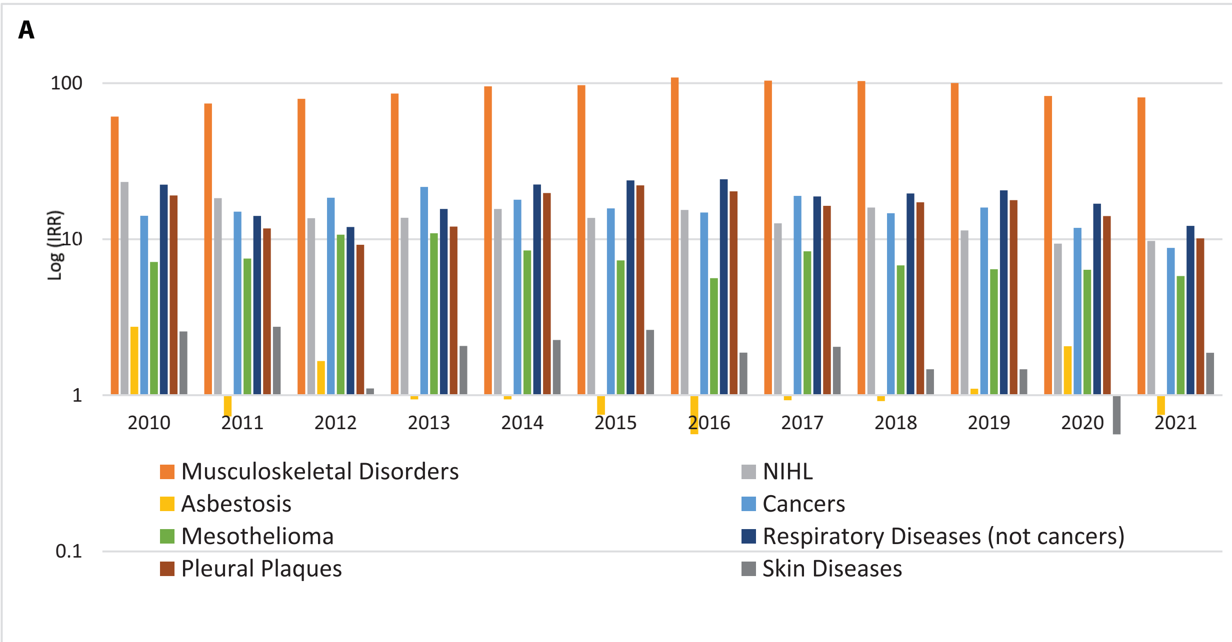
2.2. Statistics

The annual incidence of occupational diseases was calculated by dividing the number of reported ODs per year provided by INAIL [8] by the total workforce in the areas (provided by ISTAT). [8] To estimate incidence trends, the annual case numbers were analyzed using a Poisson regression model using the time (year) as a continuous variable and the estimate of the annual population of occupied workers in all sectors. Due to potential "non-consolidated numbers" of recognized ODs for the last two years considered, the model was fitted for data from 2010 to 2019. Statistical analyses were performed with StataCorp V.15. Texas, USA. A p-value for $p<0.05$ was considered significant.

3. Results

In the period considered 10,615 ODs were recognized in Friuli-Venezia Region (Figure 1a), 6,568 in Liguria region (Figure 1b) and 257,715 in Italy (Figure 2), while the overall workforce was in mean

a) Friuli - Venezia Giulia



b) Liguria

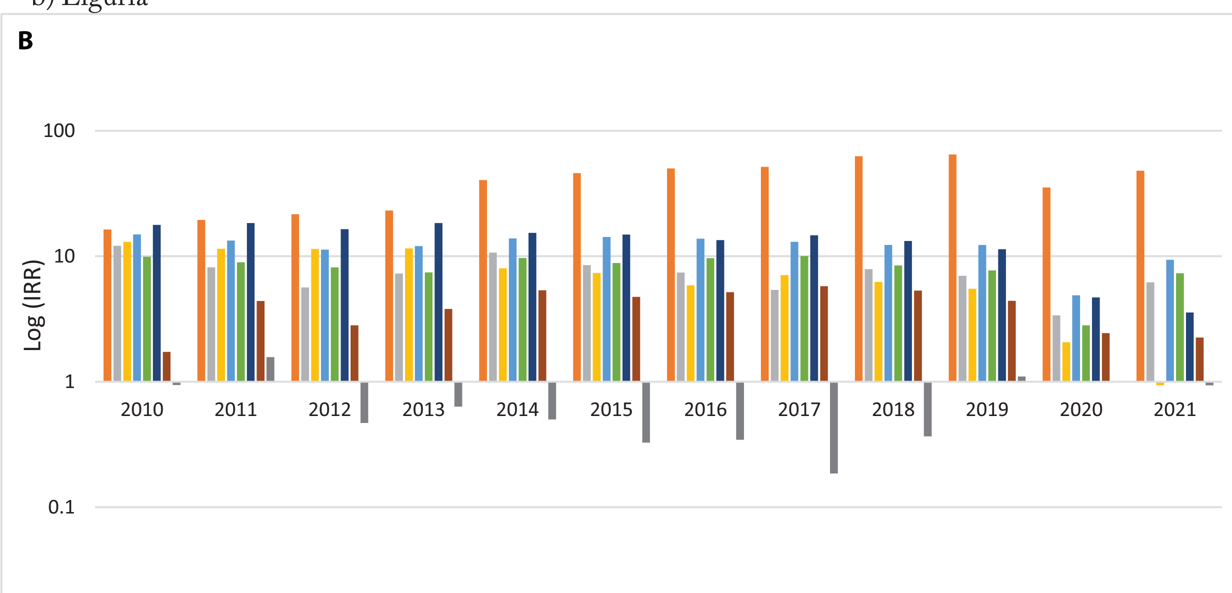


Figure 1. Incidence cases per 100,000 workers of Occupational diseases in Friuli-Venezia Giulia (a) and Liguria (b) regions from 2010 to 2021 on a semi-logarithmic scale to keep on the same graph incidences differing by orders of magnitude.

537,967, 669,433 and 22,428,333 workers in FVG, Liguria and Italy, respectively. Both Figures 1 and 2 showed an increase of incidence for MSDs from 2010 to 2016 and then a slow decrease in more recent years. To note that data on ODs in the last two years are non-completely consolidated, thou it is possible an increase of numbers due to late recognizing for more recent ODs. In 2016 the incidence

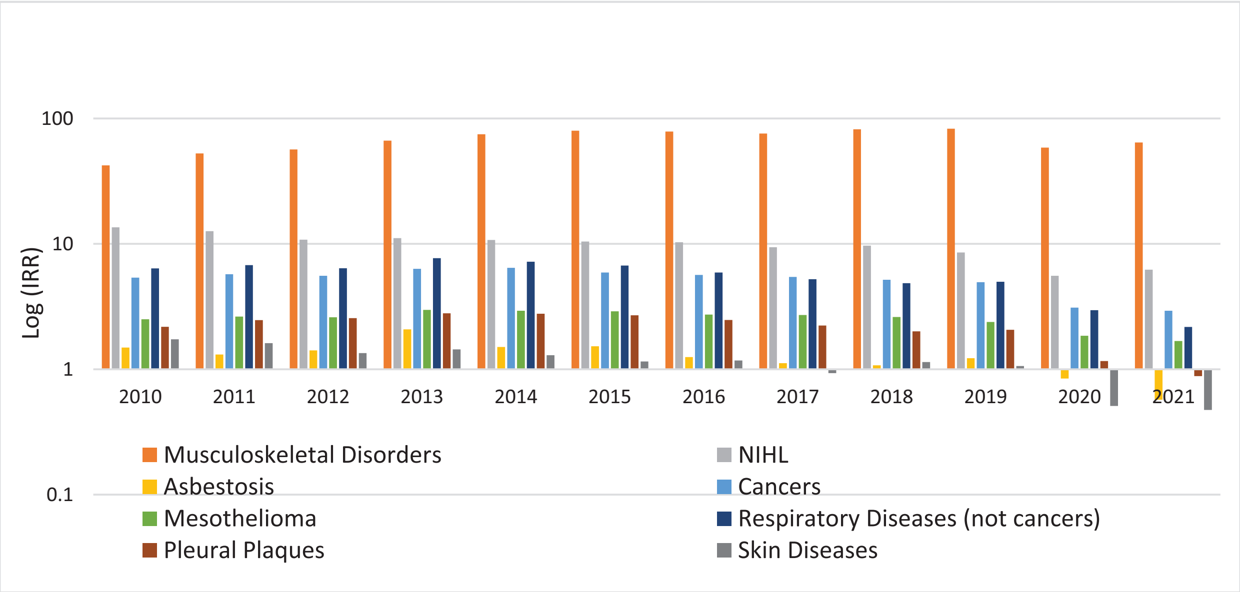


Figure 2. Incidence cases per 100,000 workers of Occupational diseases in Italy (2010-2021).

of MSDs was 109, and 78.6 cases per 100,000 workers in FVG and Italy, respectively with a decrease to 100 and 82.8 cases per 100,000 workers in 2019 and 81 and 64 cases per 100,000 workers in 2021, in FVG and Italy, respectively. In Liguria, instead, MSDs increased from 43.2 to 52 cases per 100,000 workers from 2016 to 2019. MSDs represent the 54.3% of the overall recognized ODs in FVG, the 41.7% in Liguria and the 70.9% in Italy.

Non-neoplastic respiratory diseases (that comprises pleural plaques and asbestosis) ranked second after MSDs in FVG region with a maximum in 2010 with an incidence of 22.4 cases per 100,000 workers, declining slowing to 20.6 in 2019 and to 12.2 in 2021. In Liguria the incidence was 16.9 cases per 100,000 workers in 2010, a maximum of 17.5 cases per 100,000 workers in 2013 and a declining trend until 2.87 cases per 100,000 cases in 2021. In Italy, the maximum incidence was 7.7 cases in 2013, declining to 2.2 case in 2021, well below FVG incidence.

Pleural plaques incidence ranked 3rd in FVG with 19.1 cases per 100,000 workers in 2010, 22.1 cases per 100,000 workers in 2015, 17.9 cases per 100,000 workers in 2019, declining to 10.1 cases per 100,000 workers in 2021. In Liguria incidence was ranging between 1.7 cases per 100,000 workers in 2010 to 5.7 cases per 100,000 workers in 2020. Incidence of pleural plaques in Italy was ranging around 2-2.8 cases per 100,000 workers from 2011 to 2019, declining to 0.88 cases in 2021 (Figure 3). The 12 years' incidence was 189.8, 41.9 and 16.2 cases for 100,000 workers in FVG, Liguria and Italy, respectively (11.7 times more in FVG compared to Italy).

Asbestosis incidence in FVG was ranging between 2.7 cases per 100,000 workers in 2010 (15 cases) declining to 1.9 cases per 100,000 in 2019 (6 cases). In Liguria the number of cases was much higher with an incidence of 13.1 cases per 100,000 workers in 2010 (83 cases) declining to 5.5 cases per 100,000 workers in 2019 (30 cases). In Italy asbestosis incidence was 1.5 and 1.2 cases per 100,000 workers in 2010 and 2019, respectively.

Considered the year 2019, in which INAIL data are considered completely consolidated, cancers (including mesothelioma) ranked 4th in FVG with 16 cases per 100,000 workers, with an increasing trend. In Liguria cancers ranked 3rd with 12 case per 100,000 workers. By contrast, incidence data were significantly lower in Italy with 5.2 cases per 100,000 workers in the same year.

During the period considered, 492 mesothelioma cases were recognized in the FVG region, ranging between 39 in 2010 and 58 in 2013, declining

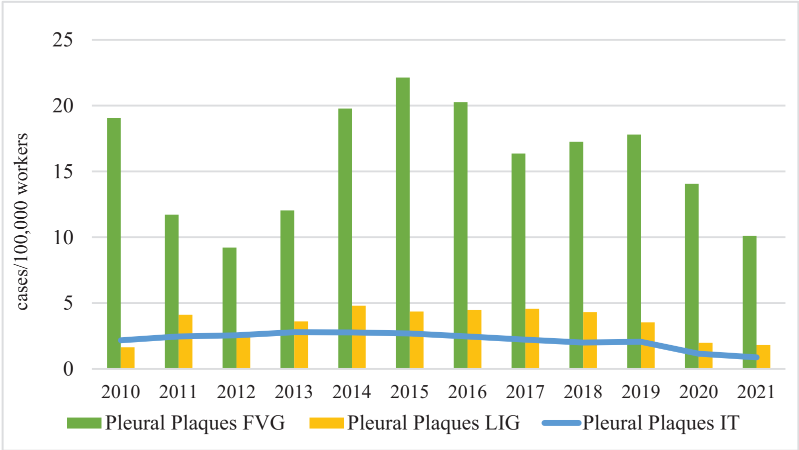


Figure 3. Incidence of Pleural Plaques in FVG Region, Liguria region and Italy (line).

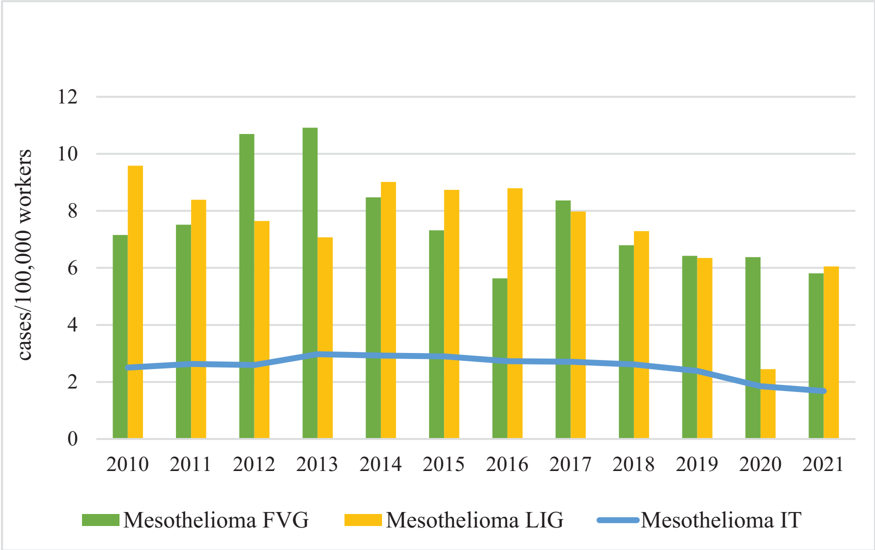


Figure 4. Incidence of Mesothelioma in FVG Region, Liguria region, and Italy (line).

progressively in recent years. Incidence was 7.1 cases per 100,000 workers in 2010 and 10.9 in 2012, declining progressively until 5.8 cases in 2021. In Liguria, 583 mesotheliomas were recognized in the period considered, with an incidence ranging from 9.9 cases per 100,000 workers in 2010 to 7.3 cases per 100,000 workers in 2021. In Italy, 6833 cases were recognized, the maximum in 2013 (650 cases) and the minimum in 2021 with 379 cases (non-consolidated data). Incidence ranged between 3.0 cases per 100,000 workers in 2013 to 1.7 cases per 100,000 workers in 2021. Figure that represents 1/3 of those registered in FVG and Liguria regions (Figure 4).

In the period considered, 76 cases of asbestosis were recognized in the FVG Region and 3447 cases in Italy, with an incidence of 2.75 and 2.06 cases per 100,000 workers in 2010 and 2020, respectively, with a fluctuation trend. In Liguria, 547 cases of asbestosis were recognized, with an incidence of 12.4 and 4.4 cases per 100,000 workers in 2010 and 2019, respectively.

Conversely, in Italy, the incidence was more constant, around 1.5 cases per 100,000 workers, with a minimum of 0.6 cases per 100,000 workers in 2021.

Noise-induced hearing loss incidence ranked 5th in the FVG region with a progressive decline to 11.4 cases per 100,000 workers in 2019 compared to 8.5 cases per 100,000 workers in Italy in the same year. In Liguria, the decline was similar, with 11.5 cases per 100,000 workers in 2010 to 5.6 cases in 2019.

The number of occupational skin diseases was low in the FVG region, Liguria, and Italy, with numbers below 3, below 1, and below 1.7 cases per 100,000 workers, respectively.

Table 1 shows the absolute number of ODs in 2010-2019 and the trend over the ten years (2010-2019) evaluated using the Poisson regression. For the FVG region, the annual change in incidence (IRR) was 1.02 (95%CI 1.01-1.03) for all diseases with a significant positive trend, maximum for MSDs 1.05 (95%CI 1.04-1.06), lower for respiratory diseases 1.03 (95%CI 1.00-1.05) and pleural plaques 1.02 (95%CI 1.00-1.06). A decreasing trend that did not reach statistical significance was demonstrated for cancers, including mesothelioma and skin diseases. The trend was significantly negative for noise-induced ear loss [0.95 (95%CI 0.93-0.97)] and asbestosis [0.90 (95%CI 0.83-0.99)]. For Liguria, an increasing trend was demonstrated for all ODs [IRR 1.07 (95%CI 1.06-1.08)], maximum for MSDs [IRR 1.17 (95%CI 1.15-1.19), lower for pleural plaques [IRR 1.07 (95%CI 1.03-1.12)]. A decreasing trend was demonstrated for NIHL, respiratory diseases, and asbestosis.

For Italy, the annual IRR was 1.03 (95%CI 1.02-1.04) for all ODs, significantly increasing for MSDs [1.06 (95%CI 1.03-1.07)]. A stable trend was shown for mesothelioma, while all other ODs are significantly decreasing, mainly skin diseases [IRR 0.94 (0.93-0.95)] and NIHL [IRR 0.96 (95%CI 0.96 to 0.97)] but also for respiratory diseases and cancers.

4. Discussion

In the present study, recognized ODs in Friuli-Venezia Giulia and Liguria regions and Italy were analyzed from 2010 to 2021, finding a significant increase in numbers mainly due to MSDs that accounted for 71% of ODs in Italy, 54% in FVG and 47.5% in Liguria. Moreover, the incidence of all analyzed ODs, was higher in the FVG region compared to Liguria and Italian data, showing important differences in ODs trends and incidence. The statistical analysis was performed from 2010 to 2019 because data are not considered stabilized for the last two years, though it is still possible to have some missing cases.

Considering ODs recognized in 2019, FVG region workers had 8.6 times more incidence of pleural plaques, 4.1 times more incidence of lung diseases, 3.2 times more incidence of cancers, 2.7 times more incidence of mesothelioma, while the overall incidence of ODs was 1.6 times more than Italian data. In Liguria, the overall incidence of ODs was lower

Table 1. Incidence of occupational diseases in Friuli-Venezia Giulia, Liguria regions and in Italy. IRR is the annual change in incidence from 2010 to 2019, assuming a linear trend. ICD-10, International Classification of Diseases; ODs, Occupational Disease; IRR, incidence rate ratio. NIHL, noise-induced hearing loss. In bold are reported significant values.

	FVG		Liguria		Italy	
Diagnosis (ICD-10)	**ODs**	**IRR (95%CI)**	**ODs**	**IRR (95%CI)**	**ODs**	**IRR (95%CI)**
Total	9 153	**1.02 (1.01-1.03)**	**5070**	**1.07 (1.06-1.08)**	223 201	**1.03 (1.03-1.04)**
MSDs (M00-M99)	4 892	**1.05 (1.04-1.06)**	**2295**	**1.17 (1.15-1.19)**	155 186	**1.06 (1.06-1.07)**
NIHL (H83.3)	829	**0.95 (0.93-0.97)**	**480**	**0.96 (0.93-0.99)**	23 987	**0.96 (0.95-0.96)**
Respiratory disease (J00-J99)	1 042	**1.03 (1.00-1.05)**	**782**	**0.95 (0.93-0.98)**	13 889	**0.96 (0.96-0.97)**
Cancers (C00-D48)	901	0.99 (0.97-1.02)	925	0.99 (0.97-1.02)	12 660	**0.99 (0.98-0.99)**
Mesothelioma (C45)	427	0.97 (0.94-1.002)	529	0.99 (0.96-1.02)	6 040	0.997 (0.99-1.01)
Asbestosis (J61)	61	**0.90 (0.83-0.99)**	**531**	**0.90 (0.87-0.93)**	3 129	**0.96 (0.95-0.96)**
Pleural plaques (J92)	892	**1.03 (1.00-1.06)**	**256**	**1.07 (1.03-1.12)**	5 424	**0.98 (0.97-0.99)**
Skin diseases (L00-L99)	109	0.96 (0.90-1.02)	39	0.91 (0.81-1.02)	2 886	**0.94 (0.93-0.95)**

than in Italy, except for asbestosis, which had a higher incidence than in Italy and the FVG region, confirming the high previous exposure to asbestos in the Liguria workforce [7].

The change in Italian legislation in 2008, the reduction of the underreporting phenomenon, and the increasing age of the workforce related to the change in retirement law in Italy caused an increase in MSDs, as already demonstrated by previous studies on claimed ODs in Italy [4, 5]. In our study, more than half of ODs are MSDs, in line with European data [1, 2], except for Scotland [10] and the Netherlands [11], in which mental diseases are the most frequent ODs. Note that for MSDs, there are differences between countries in compensation criteria, as the results trends varied widely between countries [1, 12-14].

Looking to overall incidence data of ODs (164.4, 82 and 95.7 cases per 100,000 workers in FVG, Liguria and Italy), results are lower than those reported in The Netherlands [11] in which Van der Molen found an annual incidence for claimed ODs of 346 cases (95%CI 330 to 362) per 100 000 worker-years in 2009. Oksa et al. [15] reported an incidence of recognized ODs in Finland in the period 2005-2013 of 117 cases for 100,000 with a decreasing trend. A similar incidence was reported in Poland in 1998 (117 cases per 100,000 workers) [16], decreasing to 23 cases per 100,000 workers in 2012 [17] and to 11.5 cases per 100,000 occupied workers in 2020 [18]. In the Czech Republic, Jarolímek et al. [19] reported regional differences in the incidence of ODs with a decreasing trend from 41 to 14 cases per 100,000 economically active populations in 1994 and 2013, respectively.

Compared to Italian data, our study showed a wide difference in recognized ODs in Friuli-Venezia Giulia and Liguria. This is probably due to the increased knowledge of the potential occupational causation of MSDs and asbestos-related diseases and the improvement of medical surveillance for workers linked to the Italian Law on prevention of injuries and ODs 81/2008 [20] and, for FVG, to the regional law for workers exposed to asbestos, which provides regular screening for them. The high previous exposure to asbestos in FVG and Liguria [6, 21] caused the high incidence of all asbestos related diseases included pleural plaques with an incidence increasing until 2019 (OR 1.03, 95%CI 1.00-1.06 in FVG and 1.07, 95%CI 1.03-1.12) in Liguria. On the contrary, in Italy, the incidence of pleural plaques significantly declined in the same period (OR 0.98; 95%CI 0.97-0.99).

Looking to the overall trend of ODs in Italy, MSDs are significantly increasing, as is happening in FVG and Liguria regions, mainly due to the increase in MSD recognition, while we calculated a significant decrease for NIHL, skin diseases, cancers, pleural plaques, asbestosis, and respiratory diseases. A stable trend was found for mesothelioma in Italy until 2019, with declining numbers for the last two years considered, which need to be confirmed. On the contrary, respiratory diseases (that included pleural plaques) increased until 2019 in FVG. This trend is again explained by the high former exposure to asbestos in FVG workers.

Regarding mesothelioma row incidence, FVG had 6.4 cases per 100,000 workers (2.88 cases per 100,000 inhabitants), while Italy had 2.38 cases per 100,000 workers (0.92 cases per 100,000 inhabitants). In the USA, the incidence ranges between 0.5 and 1.3 per 100,000 people [22] in northern Europe, the incidence is around 1.4 cases per 100,000 inhabitants, in Australia and New Zealand, the incidence is around 1.3 cases per 100,000 inhabitants [23-24]. In areas without asbestos exposure, the incidence of mesothelioma is estimated to be around 0.3 cases per 100,000 inhabitants [24]. Our data confirmed a higher incidence of asbestos-related diseases in the two regions considered. The numbers of mesotheliomas recognized by INAIL were lower than cases reported in RENAM (Registro Nazionale dei Mesoteliomi) [25] as expected, because not all cases of mesothelioma occurred have to be considered occupational.

Cases of asbestosis are still reported in Italy, with a declining trend from 2010 to 2019, despite the asbestos ban since 1996. Considering occupied workers in the shipyard sector (ATECO 301 from ISTAT) in 2019, the incidence of asbestosis was 6/4297 (139 cases x 100,000 workers) and 30/4985 (601 cases x 100,000 workers) in FVG and Liguria, respectively, showing wide differences. However, it is well known that asbestosis is related mainly to previous exposure to asbestos.

Moreover, the differential diagnosis between asbestosis and idiopathic pulmonary fibrosis is difficult due to similar clinical, radiological, and histopathological findings, and there is a debate in the scientific literature on the role of previous asbestos exposure and idiopathic pulmonary fibrosis, occurring many years after exposure [26]. Recently, in a case-control study performed in the UK, Reynolds et al. [26] evaluated asbestos exposure in 494 cases of idiopathic pulmonary fibrosis and 466 controls, failing to find an association with asbestos exposure.

Incidence of skin diseases decreased in the period with an overall lower incidences of skin diseases compared to international data [27-29]. Recently, Aalto-Korte et al [30] analyzing the Finnish register of occupational diseases, reported an overall incidence of 18.8 cases per 100,000 workers, much higher than our data (3 and 1.7 cases per 100,000 workers in the FVG region and Italy, respectively). It is already shown [29] that skin diseases in Italy are less reported, and incidence data are probably underestimated. Moreover, Mediterranean skin, frequently exposed to the sun, presented a lower prevalence of atopic eczema, one of the most important risk factors for contact dermatitis [29]. The decreasing trend for occupational skin diseases aligns with a European registry study [1] and EUROSTAT data [2].

NIHL decreased significantly in the FVG and Liguria regions and Italy, in accord with what is happening in other EU countries, due to better preventive actions to protect workers from noise [1].

5. Strengths and Limitations

To our knowledge, data on the incidence of ODs in Italy are limited. The comparison between two regions with a high past exposure to asbestos permitted us to highlight interesting associations. However, our study has some limitations. The first one is that available data did not allow for standardized incidence of ODs by age classes. The second limitation is the difference between reporting and recognizing ODs in Italian regions, which was expected. However, we think the apparent increase in ODs in Italy is mainly due to the decrease in the “under-reporting phenomenon” and an improved insurance system against ODs.

6. Conclusion

Our study reported the incidence of recognized ODs in Italy and the FVG and Liguria regions from 2010 to 2021, showing an increasing trend due mainly to MSDs in Italy and to MSDs, pleural plaques, and respiratory diseases in FVG. A decreasing trend was demonstrated for NIHL and dermatitis, while the incidence of mesothelioma and cancers was declining only in Italy. Wide differences in incidence were shown between FVG, Liguria, and Italy, mainly due to past asbestos exposure in the FVG region.

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

References

1. Stocks SJ, McNamee R, Van Der Molen HF, et al. Trends in incidence of occupational asthma, contact dermatitis, noise-induced hearing loss, carpal tunnel syndrome and upper limb musculoskeletal disorders in European countries from 2000 to 2012. *Occup Environ Med*. 2015;72(4):294-303.
2. EUROSTAT Why do we need the European Occupational Diseases Statistics (EODS)? https://ec.europa.eu/eurostat/web/experimental-statistics/european-occupational-diseases-statistics
3. Gittins M, Carder M, Seed MJ, Iskandar I, Daniels SAM, van Tongeren M. Improving trends estimates for specific work-related ill-health conditions when excess zeros are present in a voluntary health reporting scheme. *Occup Environ Med*. 2023;80(5):280-286. Doi: 10.1136/oemed-2022-108627. Epub 2023 Apr 3.
4. Van Der Molen HF, Marsili C, Vitali A, Colosio C. Trends in occupational diseases in the Italian agricultural sector, 2004-2017. *Occup Environ Med*. 2020;77(5):340-3. Trends in occupational disease incidence are estimated in voluntary reporting schemes such as The Health and Occupational Reporting (THOR) Network in the UK
5. Larese Filon F, Spadola O, Colosio C, Van Der Molen H. Trends in occupational diseases in industry and services sectors in Italy. *Med Lav*. 2023;114(4):e2023035.
6. Barbiero F, Zanin T, Pisa FE, et al. Cancer incidence in a cohort of asbestos-exposed workers undergoing health surveillance. *Int Arch Occup Environ Health*. 2018;91(7):831-841. Doi: 10.1007/s00420-018-1326-3. Epub 2018 Jun 5. PMID: 29869702
7. Marinaccio A, Binazzi A, Bonafede M, Di Marzio D, Scarselli A. Epidemiology of malignant mesothelioma in Italy: surveillance systems, territorial clusters

and occupations involved Regional Operating Centres. *J Thorac Dis*. 2018;10(Suppl 2):S221-S227.
8. INAIL Istituto Nazionale contro gli Infortuni sul Lavoro – Flussi informativi regionali www.inail.it/cs/internet/comunicazione/sala-stampa/comunicati-stampa/com-stampa-accordo-inail-inl-conferenza-regioni-sinp-2022.html (Last Accessed 20, March 2023)
9. ISTAT Istituto Nazionale di Statistica http://dati.istat.it/Index.aspx?DataSetCode=DICA_ACDP# (Last Accessed 05, August2023)
10. Chen Y, Turner S, McNamee R, Ramsay CN, Agius RM. The reported incidence of work-related ill-health in Scotland (2002-2003). *Occup Med* (Chic Ill). 2005;55(4):252-61.
11. Van Der Molen HF, Kuijer PPFM, Smits PBA, et al. Annual incidence of occupational diseases in economic sectors in the Netherlands. *Occup Environ Med*. 2012;69(7):519-21.
12. Carder M, Bensefa-Colas L, Mattioli S, et al. A review of occupational disease surveillance systems in Modernet countries. *Occup Med* (Lond). 2015 Nov;65(8): 615-25. Doi: 10.1093/occmed/kqv081.
13. Spreeuwers D, de Boer AG, Verbeek JH, et al. Evaluation of occupational disease surveillance in six EU countries. *Occup Med*. 2010;60:509-16.
14. European Commission. Communication from the commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of Regions. Safer and Healthier Work for All - Modernisation of the EU Occupational Safety and Health Legislation and Policy. Brussels: COM(2017) 12 Final, 2017.
15. Oksa P, Sauni R, Talola N, et al. Trends in occupational diseases in Finland, 1975-2013: a register study. *BMJ Open*. 2019;9(4):e024040. Doi: 10.1136/bmjopen-2018-024040
16. Szeszenia-Dabrowska N, Szymczak W. Incidence of occupational diseases in Poland. *Med Pr*. 1999;50(6):479-96.
17. Wilczyńska U, Sobala W, Szeszenia-Dabrowska N [Occupational diseases in Poland, 2012] *Med Pr*. 2013;64(3):317-26.
18. Świątkowska B, Hanke W. [Occupational diseases in Poland in 2020]. *Med Pr*. 2022 Dec 6;73(5):427-433 Doi: 10.13075/mp.5893.01295. Epub 2022 Nov 30.
19. Jarolímek J, Urban P. Twenty-year development of occupational diseases in the Czech Republic: medical and geographical aspects. *Cent Eur J Public Health*. 2014;22(4):251-6. Doi: 10.21101/cejph.a4063.
20. Decreto Legislativo T.U. 81/2008 https://www.gazzettaufficiale.it/eli/id/2008/04/30/008G0104/sg
21. Barbiero F, Giangreco M, Pisa FE, et al. Standardization of incidence rates of mesothelioma in the absence of national standards: sensitivity analysis in a cohort formerly exposed to asbestos. *Med Lav*. 2016;107(4):307-14.
22. Asbestos. https://www.asbestos.com/mesothelioma/incidence/#worldwide-trends (accessed 1 June 2023)
23. Binazzi A, Di Marzio D, Verardo M, et al. Asbestos Exposure and Malignant Mesothelioma in Construction Workers-Epidemiological Remarks by the Italian National Mesothelioma Registry (ReNaM). *Int J Environ Res Public Health*. 2021;19(1):235. Doi: 10.3390/ijerph19010235
24. International Agency for Research on Cancer (IARC). Cancer Today. Data Visualization Tools for Exploring the Global Cancer Burden in 2020. Available online: https://gco.iarc.fr/today/home (Last Accessed on 1 June 2023)
25. Registro Nazionale dei Mesoteliomi (RENAM) https://www.inail.it/cs/internet/attivita/ricerca-e-tecnologia/area-salute-sul-lavoro/sorveglianza-epidemiologica-negli-ambienti-di-lavoro-e-di-vita/renam.html (Last Accessed on 12 August, 2023)
26. Reynolds CJ, Sisodia R, Barber C, et al. What role for asbestos in idiopathic pulmonary fibrosis? Findings from the IPF job exposures case-control study. *Occup Environ Med*. 2023;80(2):97-103. Doi: 10.1136/oemed-2022-108404. Epub 2023 Jan 12
27. Shakik S, Arrandale V, Holness DL, et al. Dermatitis among workers in Ontario: results from the Occupational Disease Surveillance System. *Occup Environ Med*. 2019;76(9):625-631. Doi: 10.1136/oemed-2018-105667.
28. Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health*. 1999;72: 496-506.
29. Larese Filon F, Pesce M, Paulo MS, et al. Incidence of occupational contact dermatitis in healthcare workers: a systematic review. *J Eur Acad Dermatol Venereol*. 2021 Jun;35(6):1285-1289. Doi: 10.1111/jdv.17096
30. Aalto-Korte K, Koskela K, Pesonen M. 12-year data on skin diseases in the Finnish Register of Occupational Diseases II: Risk occupations with special reference to allergic contact dermatitis. *Contact Dermatitis*. 2020 Jun;82(6):343-349. Doi: 10.1111/cod.13510. Epub 2020 Apr 2.

La Medicina del Lavoro

Original article

Med Lav 2023; 114 (5): e2023043
DOI: 10.23749/mdl.v114i5.14504

Developing a Feasible Integrated Framework for Occupational Heat Stress Protection: A Step Towards Safer Working Environments

George A. Gourzoulidis[1*], Flora Gofa[2], Leonidas G. Ioannou[3], Ioannis Konstantakopoulos[4], Andreas D. Flouris[3]

[1]Research & Measurements Center of Occupational Health and Safety Hazardous Agents, Hellenic Ministry of Labour and Social Affairs, Greece
[2]Hellenic National Meteorological Service (HNMS), Greece
[3]FAME Laboratory, Department of Physical Education and Sport Science, University of Thessaly, Greece
[4]Department of National Focal Point & OSH promotion policies/National Focal Point of EU-OSHA, Hellenic Ministry of Labour and Social Affairs, Athens

Keywords: Occupational Heat Stress; WBGT Index; Occupational Health and Safety (OHS); Climate Crisis

Abstract

Background: *Specialized occupational health and safety (OHS) issues are covered at the EU level through detailed legislation and guidelines. Unfortunately, this does not extend to occupational heat stress, not only in Greece but also (with few exceptions) internationally. One possible explanation could be the difficulty in accurately identifying the dangerous conditions, as many environmental and individualized elements are involved, and hundreds of "thermal stress indicators" are available. Another explanation could be the difficulty in adequately measuring hazardous conditions for workers affected more (i.e., outdoor and high intensity) since the biological protection framework is based on the human body's internal temperature.* **Methods:** *The Wet Bulb Globe Temperature (WBGT) has been proposed as the most efficacious thermal stress indicator. Since 2021, the Hellenic National Meteorological Service has provided 48-h WBGT forecast predictions to serve as a first level of alert. Real-time measurements and 48-h forecasts of WBGT are also available through a smartphone application. Additionally, as revealed when developing the occupational heat stress legislation in Cyprus and Qatar, crucial first steps are identifying the specific characteristics of worker exposure and the tripartite collaboration between employers, workers, and the State.* **Results:** *Evaluating the simplified WBGT forecasted values and the smartphone application estimates proved well-established. The sound scientific basis can be effectively combined with administrative measures based on the EU OHS legislative experience to produce practical solutions.* **Conclusions:** *As the climate crisis exacerbates, worker productivity and well-being will decline, underscoring the urgent need for an integrated protection framework. Such a framework is proposed here.*

1. Introduction

Occupational Health and Safety (OHS) is a large interdisciplinary field that deals with almost every human activity. In its recent strategic framework 2021-7 [1], the European Commission describes a set of key actions in the changing and challenging world of work. The previous strategic frameworks

Received 22.02.2023 – Accepted 28.08.2023
*Corresponding Author: George A Gourzoulidis; E-mail: ggourz@yahoo.com

have brought significant progress in the last three decades concerning a 70% decrease of fatal accidents at work in the EU (from about 6 per 100,000 employed persons in 1994 to less than 2 in 2018), while the main focus remains on deaths from work-related illnesses that are many more (~200,000 in 2018) than the fatal accidents (3,300 fatal accidents and 3.1 million non-fatal accidents in the EU-27 in 2018). Besides health and well-being, there is also an enormous cost to the EU economy from work-related accidents and illnesses, amounting to over 3.3% of GDP annually (460 billion € in 2019) [1].

Thermal stress causes accidents as well as illnesses that can be fatal [2]. It's worth noting that, while there are Directives and/or Guidelines that cover most of the highly specialized OHS issues (i.e. vibrations, electromagnetic fields – EMF, artificial optical radiation – AOR, most of the chemical and biological hazardous agents, including SARS-CoV-2), occupational heat stress has not been adequately addressed not only in Greece but also internationally (with the exception of Cyprus, Qatar, China and Malaysia) and is covered only by relevant circulars published at the beginning of each summer. Technical (e.g. increased intake of water and electrolytes, clothing) and organizational (e.g. shifting work to cooler hours) best practices are employed [3-5], combined with risk assessment techniques [6-8]; all these can be also used for employee training. Not all workers are affected in the same way; outdoor, high intensity and intrinsic heat exposure are the main categories to deal with.

The above-mentioned discrepancies arise from the difficulties to accurately define the dangerous conditions, which is an aspect of uncertainty, since many environmental and individualized parameters are involved. For this reason, hundreds of relevant 'thermal stress indicators' exist, as revealed from a recent systematic review [9]. More specifically, a total of 340 thermal stress indicators have been developed, 153 of which are of no practical significance for large-scale guidance for occupational settings because they are nomograms, arcane instruments, and/or require detailed non-meteorological information (e.g. metabolic rate, clothing insulation, type of work). Concerning the remaining 187 indicators that are based only on meteorological data (i.e. air temperature, relative humidity, solar radiation, wind speed), 126 are primarily designed for sports and physical exercise, while the remaining 61 apply to workplaces and have been designed to detect occupational heat/cold stress [9].

The benchmark and simplest, meteorological index to apply is air temperature. Ten years ago in Greece, three different collective agreements existed (construction, couriers and ship repair), which included three different air temperature limits to protect workers against heat stress (36, 37 and 38°C). This non-scientific approach is no longer in use due to the cessation of collective agreements during the years of the recent economic crisis in Greece.

These 61 thermal stress indicators provide different approaches to estimate the 'perceived temperature' that is a combination of the environmental conditions with the biological parameters of thermoregulation, workload, clothing, acclimatization, etc. Human thermoregulation is a highly specialized survival mechanism, capable of coping with all the aforementioned issues through autonomic (i.e. implementing vasodilation, sweating, and increased respiratory rate in hot environments) and behavioral (i.e. by reducing clothing and physical activity) reactions [10]. While approaches such as the Physiological Heat Strain (PHS) model, described in ISO 7933, allow for detailed analysis of the physiological response of individuals exposed to thermal stress, their use in large-scale assessment and guidance remains limited [11, 12]. A recent multi-country field assessment concerning the 61 thermal stress indicators for occupational settings demonstrated that the empirical index of Wet Bulb Globe Temperature (WBGT) is the most efficacious thermal stress indicator in order to apply quick, large-scale assessment [9, 13, 14].

Another possible explanation of the limited adoption of legal frameworks to protect against occupational heat stress could be the difficulty to accurately measure the dangerous conditions, as the biological protection framework is based on the core temperature of the human body, allowing up to a 1°C increase [15]. Nevertheless, as previously mentioned, the choice of the proper occupational heat stress index is moving towards WBGT, while its measurement and/or prediction is now technically feasible as smartphone apps are an increasingly viable option to facilitate communication. Additionally, other models like the PHS model [11] allow much more detailed assessment. In this sense the most plausible explanation of the delay seems to be the lack of an integrated protection framework.

As the climate crisis continues to exacerbate environmental conditions [16], it is clear that its consequences involve not only the health but also the productivity of the workers [17]; an evaluation of recent European heat-waves determined an annual cost of €160 billion due to these causes [17]. At an EU level, the recent HEAT-SHIELD project funded by the European Commission proposed an early warning system which uses WBGT, vulnerability, and exposure information to produce short- and long-term advice on heat-management strategies [18]. In Greece, the active collaboration of the Hellenic Ministry of Labour and Social Affairs with the stakeholders (workers' and employers' organizations), the Hellenic National Meteorological Service (HNMS) and the Environmental Physiology FAME Lab of the University of Thessaly, has produced such an integrated protection framework that is briefly presented in the Discussion section.

2. Methods

2.1. The WBGT Index

The choice of the WBGT as a thermal stress indicator has been common for several decades [19], and it was further supported by a recent field assessment in occupational settings [9, 13, 14]. WBGT can be used both for outdoor and indoor assessments and is defined accordingly as follows (1):

$$WBGT_{outdoor} = 0.7\,T_{nwb} + 0.2\,T_g + 0.1\,T_a \text{ and}$$
$$WBGT_{indoor} = 0.7\,T_{nwb} + 0.3\,T_g \quad (1)$$

where: T_{nwb} is the natural wet bulb temperature, measured by a thermometer yarn in distilled water and exposed to the thermal radiation and to the wind, T_g is the globe temperature, measured inside a black sphere and T_a is the air temperature (dry temperature). As mentioned above, T_a alone is not an effective thermal stress indicator, because it cannot account for conditions of low wind, high humidity, and/or high solar radiation [10]. The WBGT index implies various work-rest schemes considering environmental conditions, metabolic rate, clothing and acclimatization, in order to prevent occupational heat stress [15]. Moreover, it has been also used for the general public concerning climate change [20].

In a typical weather station, only the air temperature and the relative humidity are measured using shaded meteorological devices. In this sense, the T_{nwb} and T_g temperatures cannot be accurately specified, and approximations of the WBGT are used. In our work, the Liljegren approximation (WBGT-Lil) and the simplified methodology of the American College of Sports Medicine (WBGT-Sim) [21] have been chosen as the best options. Liljegren [22] developed an approximation independent of the applied location model, comprising the mass-energy equilibrium equations, where T_g includes direct and diffuse sunlight, making the method applicable in sunshine and heavy clouds. The mathematical formulation is complex and is supported by relevant software. In cases where only air temperature and relative humidity (RH) measurements are available, the simplified equation (2) is also applicable [21]. While this was initially developed for shaded indoor or outdoor locations, it has also been extensively used for outdoor locations exposed to direct sunlight (VP stands for vapor pressure, DW for dew point and RH for relative humidity, and T_a for air temperature):

$$WBGT\text{-}Sim = 0.567 \times T_a + 0.393 \times VP + 3.94 \quad (2)$$

where: $VP = 6.11 \times 10^{(7.5 \times DW)/(237.3 + DW)}$ and

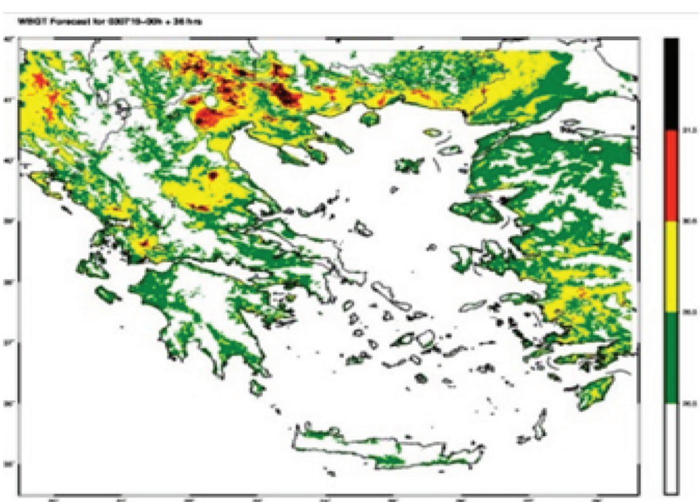
$$DW = 273.3 \frac{\dfrac{\log \frac{RH}{100}}{17.27} + \dfrac{T_a}{273.3 + T_a}}{1 - \dfrac{\log \frac{RH}{100}}{17.27} - \dfrac{T_a}{273.3 + T_a}}$$

It is worth mentioning that the WBGT estimation accuracy is limited by measurement errors associated with the omission of global temperature in calculations as well as errors associated with instrumentation and calibration procedures. The WBGT measuring devices nowadays are fairly small and practical, since they implement a much smaller (than the standard) black globe, and they do not include a natural wet bulb temperature meter which is replaced by an anemometer that improves accuracy. The ISO 7726 and ISO 7243 set an acceptable accuracy of ±0.5°C when measuring WBGT [23, 24].

2.2. WBGT Prediction by the Hellenic National Meteorological Service

In order to predict WBGT values (Figure 1), forecasted values from the HNMS's Numerical Weather Prediction (NWP) model COSMO-GR1 for a number of weather parameters were used. COSMO-GR1 is a non-hydrostatic regional model that was developed by the COSMO consortium (COnsortium for Small-scale MOdeling, www.cosmo-model.org). The horizontal resolution used in this application is 0.01° (~ 1 km) and the grid covers horizontally the Hellenic region and includes 80 vertical layers. Boundary conditions are embedded on a daily basis from the ECMWF (European Center of Medium Range Forecast) and the corresponding dimension of the matrix for every forecasted parameter is 800x1000 points. On a daily basis, hourly predictions of various parameters (wind speed, 2m temperature, 2m dew point, solar radiation, etc.) are extracted for a 48h forecast horizon. Those values are used as input for the WBGT-Lil calculation algorithm, especially developed for this study that is based on the R libraries that were developed by Ana Casanueva of the Swiss Meteorological Service for the EU-funded HEAT-SHIELD project (www.heat-shield.eu).

As with any numerical product, WBGT forecasts are associated with errors. The accuracy of the calculations depends highly on the reliability of the forecasted parameters that are inserted in the algorithms that produce WBGT predictions. It should be noted that on average, the two main parameters in the calculations (2m temperature and dew point) are associated with errors of about 0.5 degrees with a clear diurnal cycle in error phase [25] which is inherited unavoidably to WBGT predictions. At the current stage, WBGT is not used to screen work activities but as an alert to set the OHS procedure. Given that this is a general guidance provided by the HNMS for the entire population, it does not provide details in relation to work intensity, clothing, and acclimatization.



Risk Level	WBG T (°C) Min	Max
1	<26.6	26.6
2	26.7	29.4
3	29.5	31.1
4	31.2	32.2
5	32.3	>32.3

Figure 1. Indicative WBGT predictions map produced by HNMS in 1km resolution, applying the Liljegren algorithm and adapted in color scale (left). Color scale of WBGT risk level (right) is a simplification approach, while detailed information is included in the circular.

2.3. The WBGT Prediction Application for Smartphones

FAME Lab has developed a WBGT prediction application for smartphones. It obtains precise geolocation through Application Programming Interfaces (APIs) to the OpenWeather web service (www.openweathermap.org), which offers weather data from satellite and weather stations for more than 200,000 cities worldwide. Solar radiation is calculated through mathematical models that consider the exact geographical and time location, while an estimation of the cloudiness percentage is also carried out based on relevant literature. Four meteorological parameters (air temperature, relative humidity, wind speed, and solar radiation) are used to estimate WBGT according to Liljegren's approach.

As the mathematical approach (WBGT-Lil) has been repeatedly validated, the accuracy and validity of the application depend on the proximity to the weather station and on the reliability of the available environmental data. To test this hypothesis by quantifying the relative error, the FAME Lab collected WBGT measurements all over Greece using portable weather stations (Kestrel 5400FW, Nielsen-Kellerman, Pennsylvania, USA), which were compared to the simultaneous use of the WBGT app at the point of assessment.

2.4. The Cases of Cyprus and Qatar

In Cyprus, an organized effort to mitigate workers' heat stress was launched over 10 years ago. An extensive code of practice (as well as a short one) was issued in 2014, with the parallel adoption of three indices (Corrected Active Temperature, Heat Stress Index, Sensible Temperature), which are calculated through measurements carried out by employers in the workplace with low-cost thermo-hygrometers [26]. Key parts of this effort were the cooperation of all productive entities and the pilot implementation phase until it reached the point of active legislation.

At the same time, in Qatar, known for its high temperatures, no extensive research had been conducted, as in any other Persian Gulf country, to assess whether and to what extent these high heat levels affect workers. Adopting countermeasures created for other countries (e.g., for the USA) may not be effective and, more importantly, may have disastrous consequences if used in significantly different settings. It was, therefore, vital to conduct a broad evaluation, in real field conditions, to test different countermeasures and provide specific guidance to the stakeholders. In 2019, the International Labour Organization and the Qatar Ministry of Labour commissioned FAME Lab to conduct a large study on occupational heat stress focusing on outdoor manual work (https://bit.ly/3JQzDGF). Data concerning mental and physical health, physiology, and work effort per second of the workers, were collected for more than 5,500 hours of work. The effectiveness of different coping strategies regarding environmental conditions was also compared. Although high heat levels were recorded, workers could perform their work safely when effective heat stress measures were in place, and very few experienced short-term high body temperatures. Some of the applied measures were:

- Workers were able to regulate work intensity and take frequent breaks;
- The importance of effective hydration strategies was highlighted as many workers were found to be dehydrated from the beginning of their shift;
- It was found that workers are more likely to avoid hyperthermia if they replace dark-colored overalls with loose, light-colored clothing made of breathable fabrics.

This research provided the scientific basis to propose adjustments to Qatar's existing relevant legislation and evaluated their effectiveness (https://bit.ly/3yGnyiY), so in May 2021 new legislation was announced that adopted all research proposals. The measures included, among others, adopting the WBGT index so that outdoor work must be stopped when 32.1°C is exceeded. As recently announced by the International Labor Organization [27], within the first year of its implementation, the package of measures led to a more than 50% reduction in workers' hospitalization for health problems related to heat stress, without limiting productivity.

3. Results - Evaluation

3.1. How Close are the HNMS Forecasted WBGT Values to the Observed Values?

Up to now, specialized WBGT instruments are not included in the standard equipment of meteorological stations, even worldwide. For this study, measurements were made in the framework of the collaboration of HNMS with the Hellenic Ministry of Labour and Social Affairs, while the equipment was provided by the FAME Lab. Specifically, WBGT instruments were placed near the meteorological stations at several airport locations. An experimental campaign took place during the summer of 2019, i.e. from the end of May through early September. The collected and analyzed data were used for the evaluation of WBGT forecasts derived from the HNMS that is, it was possible to have WBGT measurements, which can be compared to the predicted simplified values.

Before the operational use of any numerical forecast product, a statistical evaluation of its error range is necessary in order to quantify the deviations compared to the observations. Bias (prediction-observation) and Root Mean Square Error (RMSE) indices were used in the statistical analysis and their values are provided in Figure 2 [28].

The BIAS diagram (Figure 2), shows the difference between predicted and observed WBGT values for the three summer months. The mean BIAS is +1.87°C (overestimation) for WBGT-Sim predictions and −1.15°C (underestimation) for WBGT-Lil, when using the methodology developed. Accordingly, the average value of RMSE is 3.74 and 2.42, suggesting that the use of the more sophisticated formula (Liljgren) allows more reliable prediction of the index. While this magnitude of error in WBGT predictions is similar to that inherited from temperature errors in numerical predictions as mentioned in section 2.2, it exceeds the ±0.5°C recommendation set in ISO 7726 and ISO 7243 when measuring WBGT in situ [23, 24]. However, it is important to note that these are forecasts with a 48-hour horizon and not real-time observations. Based on this notion and considering that additional work in the future will increase our sample size and thus improve accuracy, WBGT forecasts are considered reliable for any use.

3.2. WBGT In-situ Measurements and the WBGT Application-Derived Values

The WBGT measurements performed by FAME Lab showed that the estimation of the WBGT index through the WBGT application shows a very strong

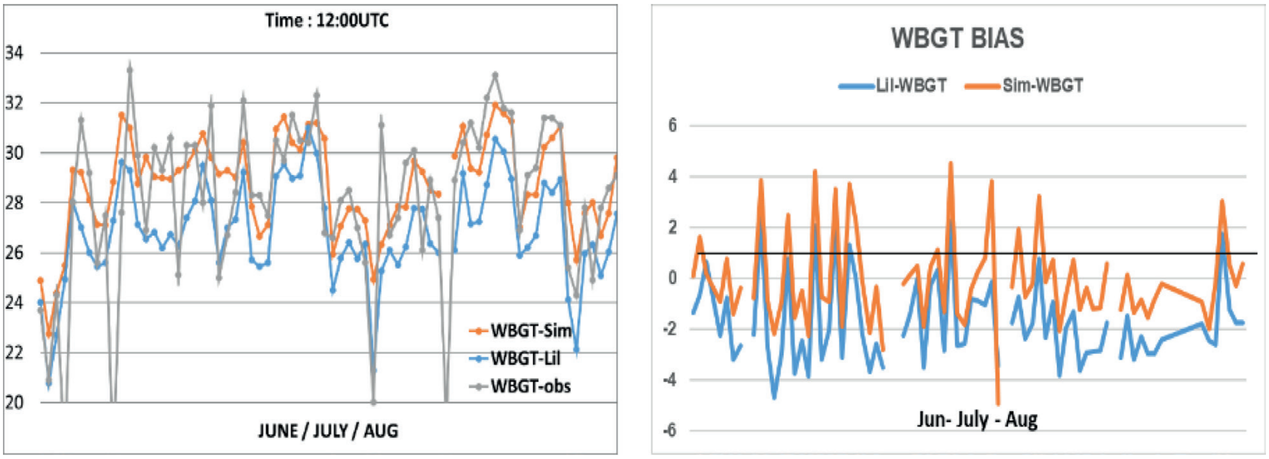


Figure 2. Time series of WBGT-Lil, WBGT-Sim forecasts and WBGT-obs observations (left) and plot of forecasted values Bias (right).

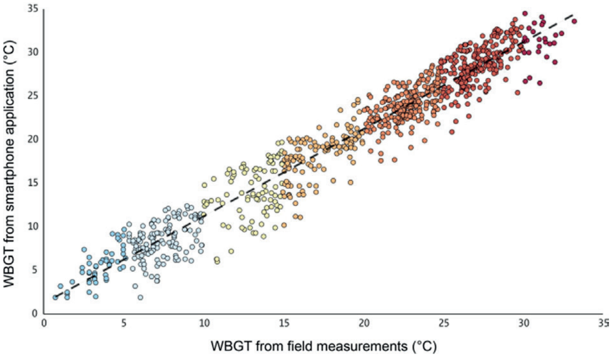


Figure 3. Differences between the estimation of the WBGT index through the WBGT application and the actual measured values, at the same geographical point. The prediction slightly underestimating (–1.2 °C) the actual readings. Each circle reflects a measurement at a different location. The colors indicate the six categories of thermal stress based on a 5-point scale from 1-5 (cold) to 31-35 (hot).

correlation (R^2=0.94, p<0.001) with the actual field measurements made using portable weather stations (Kestrel 5400FW, Nielsen-Kellerman, Pennsylvania, USA), slightly underestimating (–1.2°C) the actual readings (Figure 3). As above, given that these are estimations from the closest weather station as well as forecasts with a 48-hour horizon, this level of accuracy is considered acceptable. This is especially true considering that additional work in the future will increase our sample size and thus improve accuracy.

4. Discussion - An Integrated Protection Framework

As the cases of Qatar and Cyprus demonstrate, although vital, the forecasting and measurement procedures are only part of the overall management of occupational heat stress. A comprehensive protection framework should include the following steps and/or key points:

- The corresponding assessment of the general population does not effectively address the assessment of occupational thermal stress. Forecasts and/or warnings are used as guidance for workers, but the subsequent steps are different;

Table 1. Upper and lower action values (°C WBGT) in relation to metabolic rate in Watts [30]. The lower action value indicates the upper WBGT value that work can continue. The upper action value is the WBGT value where work stops.

Metabolic rate (W)	lower action values	upper action values
Low (180)[1]	31.0	32.5
Moderate (300)[1]	28.0	31.5
High (415)[2]	27.5	30.5
Very high (520)[3]	28.0	30.0

Note: [1] = work can continue without interruption; [2] = work can continue with 15 min break every hour; [3] = work can continue work can continue with 30 min break every hour.

- Occupational thermal stress is treated as a hazardous Occupational Health and Safety (OHS) agent, for which the employer must take a series of prescribed measures [29]. Therefore:
  1. Thermal stress must be considered in the written risk assessment;
  2. It must be certified that there is a relevant provision if measurements are required;
  3. It should be ensured that there is information, training, consultation, and participation of workers, as well as surveillance of their health and provision for sensitive groups. In general, typical office work does not require special measures, but for work performed outdoors, with inherent heat exposure, physical activity, and/or use of protective clothing, provisions should be made based on the following measures;
- The WBGT index is chosen as the bioclimatic indicator of foreseeable risks to model a forecasting system useful to identify alert and risk situations in advance. This type of approach cannot replace a risk assessment targeted at a specific occupational exposure situation;
- Following the rationale of EU Directives, it is proposed to adopt an exposure limit value and action exposure values (Table 1) for the

Table 2. Work-resting schemes in relation to metabolic rate [30, 31]. The lower action value indicates the upper WBGT value that work can continue without interruption.

Time every 60 min of work (min)		°C WBGT over the lower action value – metabolic rate			
Work	**Resting**	**Low**	**Moderate**	**High**	**Very High**
60	0	31	28	*	*
Up to 45	At least 15	31	29	27.5	*
Up to 30	At least 30	32	30	29	28
Up to 15	At least 45	32.5	31.5	30.5	30
Complete work interruption		>32.5	>31.5	>30.5	>30

** Accurate assessment of heat stress with core body temperature measurements is required.*

various heat exposure levels, based on the WBGT, as follows:

1. The exposure limit value is defined as the increase in the worker's core body temperature to 38°C, i.e. an increase of 1°C above normal [15].
2. In order to ensure compliance with the exposure limit value, which is difficult to control, directly measurable upper and lower action values are defined (Table 1) [30]. The lower action value indicates the upper WBGT value that work can continue without interruption. The upper action value is the WBGT value where work stops.
3. When heat exposure exceeds the lower action values, the employer sets the organization on alert, e.g. makes personal protective equipment (PPE) available to employees. When the exposure exceeds the upper action values, either the work stops, or additional measures are taken, or the area is marked with appropriate signs for access only by workers with appropriate training and/or PPE. Various work-resting schemes are applied for intermediate values (Table 2) [30, 31].

- Determining the actual workers' exposure considers the exposure limit value reduction due to a possible lack of acclimatization. Acclimatization is considered sufficient if, during the previous 15 days, 12 or more 8-hour shifts have been performed in the environmental conditions under investigation. Otherwise, a 2.5°C reduction is applied to the upper/lower action value. At the beginning of summer, all workers are considered non-acclimatized. Corresponding corrections are provided for the metabolic rate and the PPE (e.g., clothing) likely to be worn by the worker [15], i.e.:
- Upper/Lower action value = WBGT action value according to metabolic rate - WBGT according to personal protective equipment - WBGT according to acclimatization level (3)
- The simplified WBGT forecast, now provided by HNMS for 24/48h, can be used by the organizations to plan OHS measures;
- Calculation/prediction of WBGT, provided by the free WBGT application, can be valuable but cannot – at this point in time – act as an *in situ* assessment. If additional data in the future allow reduction of the bias to no more than 0.5°C WBGT, the free WBGT application could act as an in situ assessment;
- The prediction margins are of the order of 1° C (even a little more) that is sufficient to initiate the alert procedure; apart from the ± 0.5° C demand for the WBGT measurements there are many more uncertainty factors. Specialized in situ measurements are much more indicative.
- To calculate the WBGT, in addition to specialized measurements, the widely accepted simplified equation (2) can be used for indoor and outdoor locations, in cases where only air temperature and relative humidity measurements are available. Automatic calculation of the simplified index is provided at the link: www.famelab.gr/el/meteo. Those measurements/

calculations can be easily carried out by the employer and/or the Safety Officer;
- Registration of the above procedure shall facilitate the relevant compliance control by the competent Authorities.

A circular based on this approach was issued before the summer of 2022 by the Hellenic Ministry of Labour and Social Affairs [32], and a pilot phase was launched in the summer of 2021. The legal integration of the whole procedure is the next crucial step. The knowledge already gathered indicates that this final step mainly relies upon political will. A recently introduced legislation based on methodologies similar to those presented here demonstrated, within the first year of its implementation, a more than 50% reduction in worker hospitalization for health problems related to heat stress, without limiting productivity [27]. Future research in Greece will validate the prediction model accuracy and provide real heat exposure data and stop-down times from the implemented pilot phases.

5. Conclusions

The unresolved OHS issue of heat stress has taken on greater significance in light of the climate crisis. New ideas and solutions have been combined to promote an integrated framework. The scientific background is based on the well-established WBGT index, which was demonstrated to be able to support the general assessment. More specifically, the different formulas to calculate WBGT [the complete equation (1), the simplified equation (2), and Liljegren's approach], enable a 48 h forecast by the Hellenic National Meteorological Service, which is complemented by the smartphone application provided by FAME Lab. More specific occupational exposures can be performed using more detailed approaches if indicated by the written risk assessment. The administrative framework, based on the rationale of relevant OHS Directives, to support and unify the scientific background is briefly presented, which led to the Hellenic Ministry of Labour and Social Affairs issuing a circular based on this approach in the summer of 2022.

Acknowledgments: We would to express our gratitude to the ex Labour Minister Efi Achtsioglou for setting up the procedure that is described here and to the General Director of labour relations, health and safety at work and integration into work, Konstantino Agrapida for actively supporting the effort.

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

References

1. European Commission (EC), 'EU Strategic framework on health and safety at work 2021-2027', COM(2021) 323 final, Brussels.
2. Flouris AD, Dinas PC, Ioannou LG, et al. Workers' health and productivity under occupational heat strain: a systematic review and meta-analysis. *Lancet Planet Health*. 2018;2(12):521-31. Doi: 10.1016/S2542-5196(18)30237-7. PMID: 30526938
3. Hellenic Ministry of Labour and Social Affairs. 'Prevention of occupational heat stress during heatwave'. Circular 217464/6.7.2020 (reference in Greek).
4. Hellenic mining enterprises' association. 'Mining and quarry regulation', 2011 (reference in Greek).
5. Health & Safety Executive (HSE), 'Heat stress in the workplace, a brief guide', INDG451, 2013.
6. Association of Farmworker Opportunity Programs, 'TRAINER GUIDE AND WORK BOOK', 2010 Occupational Safety and Health Administration, U.S. Department of Labor.
7. Occupational Health and Safety Council of Ontario, 'HEAT STRESS AWARENESS GUIDE, 2007, 5252A CSAO (04/07), Ontario, Canada.
8. Malaysian Department of Occupational Safety and Health, 'GUIDELINES ON HEAT STRESS MANAGEMENT AT WORKPLACE', 2016, Ministry of Human Resources, Malaysia.
9. Ioannou LG, Dinas PC, Notley SR, et al. Indicators to assess physiological heat strain, part1: Systematic review, part2: Delphi exercise. *Temp*. 2022. Doi: doi.org/10.1080/23328940.2022.2044738.
10. Flouris AD. Human thermoregulation. In Heat Stress in Sport and Exercise; Périard J. and Racinais S., Eds.; Springer Nature, UK, 2019.
11. Ioannou LG, Tsoutsoubi L, Mantzios K, et al. A free software to predict heat strain according to the ISO 7933:2018. *Ind Health*. 2019;29;57(6):711-720. Doi: 10.2486/indhealth.2018-0216. Epub 2019 Mar 27. PMID: 30918161; PMCID: PMC6885605.
12. ISO 7933. 2004, Ergonomics of the thermal environment—Analytical determination and interpretation of heat stress using the predicted heat strain model. International Organization for Standardization, Geneva.

13. Ioannou LG, Tsoutsoubi L, Mantzios K, et al. Indicators to assess physiological heat strain – Part 3: Multi-country field evaluation and consensus recommendations. *Temperature* (Austin). 2022;9(3):274-291. Doi: 10.1080/23328940.2022.2044739. PMID: 36249710; PMCID: PMC9559325.
14. Ioannou LG, Dinas PC, Notley SR, et al. Indicators to assess physiological heat strain – Part 2: Delphi exercise. *Temperature* (Austin). 2022;9(3):263-273. Doi: 10.1080/23328940.2022.2044738. PMID: 36211947; PMCID: PMC9542877.
15. ISO 7243: 2017, 'Ergonomics of the thermal environment - Assessment of heat stress using the WBGT (wet bulb globe temperature) index'.
16. Georgoulias AK, Akritidis D, Kalisoras A, et al. Climate change projections for Greece in the 21st century from high-resolution EURO-CORDEX RCM simulations. *Atmos Res*. 2022;271.
17. Garcia-Leon D, Casanueva A, Standardi G, et al. Current and projected regional economic impacts of heatwaves in Europe. *Nat Commun*. 2021;5807(12). Doi: https://doi.org/10.1038/s41467-021-26050-z.
18. Morabito M, Messeri A, Noti P, et al. An Occupational Heat-Health Warning System for Europe: The HEAT-SHIELD Platform. *Int J Environ Res Public Health*. 2019:13;16(16):2890. Doi: 10.3390/ijerph16162890. PMID: 31412559; PMCID: PMC6718993.
19. Hellenic Ministry of Labour and Social Affairs. 'Handling occupational heat stress during summer'. Circular 130427/26.6.1990 (reference in Greek).
20. Lemke B and Kjellstrom T. Calculating workplace WBGT from meteorological data: a tool for climate change. *Ind Health*. 2012;50(4), 267-78.
21. American College of Sports Medicine. Prevention of thermal injuries. Position stand. *Med J Aust*. 1984; 141(12-13):876-9.
22. Liljegren JC, Carhart RA, Lawday P, et al. Modeling the wet bulb globe temperature using standard meteorological measurements. *J Occup Environ Hyg*. 2008;5: 645-655.
23. ISO 7726:1998. Ergonomics of the thermal environment—Instruments for measuring physical quantities. International Organization for Standardization, Geneva.
24. ISO 7243:2017. Ergonomics of the thermal environment — Assessment of heat stress using the WBGT (wet bulb globe temperature) index. International Organization for Standardization, Geneva.
25. Gofa F, Pytharoulis I, Andreadis T, et al. Evaluation of the Operational Numerical Weather Forecasts of the Hellenic National Meteorological Service. 9th Conference of Meteorology, Climatology and Atmospheric Physics, 9th COMECAP, Thessaloniki, 28-31 May, 2008.
26. Ministry of Labour of Cyprus. Occupational Heat Stress. Nicosia 2014 (reference in Greek).
27. ILO. One is too many. The collection & analysis of data on occupational injuries in Qatar. Doha, Qatar 2021.
28. Gofa F, Nikas D, Gourzoulidis GA and Flouris AD. Measuring and predicting heat stress conditions with the WBGT index. 15th International Conference on Meteorology, Climatology and Atmospheric Physics - COMECAP 2021.
29. Directive 89/391/EEC, on the introduction of measures to encourage improvements in the safety and health of workers at work - "Framework Directive".
30. ACGIH. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents. 2020. ISBN: 978-1-607261-12-4.
31. ISO 7243: 1989, 'Hot environment – Estimation of the heat stress on working man, based on the WBGT (wet bulb globe temperature)'.
32. Hellenic Ministry of Labour and Social Affairs. 'Handling occupational heat stress during summer'. Circular 56163/15.6.2022 (reference in Greek).

La Medicina del Lavoro

Original article

Med Lav 2023; 114 (5): e2023050
DOI: 10.23749/mdl.v114i5.15275

No Excess Total Mortality in Italy in the First Semester of 2023 at All Ages and in the Working Age Population

Gianfranco Alicandro[1,2*], Alberto G. Gerli[3], Claudia Santucci[3], Stefano Centanni[4], Giuseppe Remuzzi[5], Carlo La Vecchia[3]

[1] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
[2] Cystic Fibrosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[3] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[4] Respiratory Unit, Department of Health Sciences, ASST Santi Paolo e Carlo, Università degli Studi di Milano, Milan, Italy
[5] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy

Keywords: COVID-19; SARS-CoV-2; Pandemic; Excess Deaths; Working Age

Abstract

Background: *Italy experienced a sustained excess in total mortality between March 2020 and December 2022, resulting in approximately 226,000 excess deaths. This study extends the estimate of excess mortality in the country until June 2023, evaluating the persistence of excess mortality.* **Methods:** *We used mortality and population data from 2011 to 2019 to establish a baseline for expected deaths during the pandemic. Over-dispersed Poisson regression models were employed, stratified by sex, to predict expected deaths. These models included calendar year, age group, and a smoothed function for the day of the year as predictors. Excess mortality was then calculated for all ages and working ages (25-64 years).* **Results:** *From January to June 2023, we found a reduction in the number of deaths compared to the expected ones: 6,933 fewer deaths across all age groups and 1,768 fewer deaths in the working age category. This corresponds to a 2.1% and 5.2% decrease in mortality, respectively.* **Conclusions:** *The excess mortality observed in Italy from March to December 2022 was no longer observed in the first six months of 2023.*

1. Introduction

During the first half of 2023, there has been a global decrease in COVID-19-related deaths, hospitalizations, and intensive care unit admissions [1]. This reassuring trend, along with the high levels of population immunity to SARS-CoV-2, prompted the WHO Director-General, with the advice of the International Health Regulations (2005) Emergency Committee regarding the COVID-19 pandemic, to determine in May 2023 that COVID-19 has transitioned from being a global public health emergency to an established and ongoing health issue which no longer constitutes a public health emergency of international concern [2]. However, they also acknowledged the remaining uncertainties posed by the potential evolution of SARS-CoV-2. In this regard, some concerns arise from the recent excess mortality reported in Australia and New Zealand, countries with high vaccine uptake that did not experience excess mortality during the previous phases of the pandemic [3-5].

Thus, collecting and monitoring relevant epidemiological data on the evolution of the COVID-19 pandemic is important. In this regard, excess total mortality is a critical metric. This measure captures the discrepancy between the number of observed deaths during the pandemic and those expected based on historical data. Unlike official COVID-19 death counts –which can be influenced by varying definitions, diagnostic criteria, and potential underreporting –excess total mortality offers a

Received 09.10.2023 – Accepted 12.10.2023
*Corresponding Author: Gianfranco Alicandro; E-mail: gianfranco.alicandro@unimi.it

comprehensive and robust understanding of the pandemic's overall impact [6].

In our previous work, we estimated a total excess of approximately 100,000 deaths in Italy from March to December 2020, around 60,000 and 66,000 additional deaths in 2021 and 2022, respectively [7, 8]. This excess mortality affected not only the elderly population but also working-age individuals, with approximately 15,000 excess deaths estimated at ages 25 to 64 from March 2020 to December 2022. No further excess was instead observed in the initial months of 2023. The present study extends these analyses to cover the most recent period.

2. Methods

National daily mortality data and corresponding population data from January 1, 2011, to June 30, 2023, were retrieved from the Italian National Institute of Statistics archives [9]. We computed the difference between observed and expected deaths using a counterfactual scenario in which the COVID-19 pandemic had not occurred. Daily expected deaths were estimated separately for men and women using an over-dispersed Poisson regression model. The model included a linear term for the calendar year to account for temporal trends in mortality, age groups (<1, 1-4, 5-9, ..., ≥100 years) to consider the effect of age on mortality rate and a natural spline function of the day of the year to capture seasonal variations. To account for changes in the population's demographic size and age structure, the model included the natural logarithm of the population as an offset term. The number of knots in the spline function was selected based on the quasi-Akaike Information Criterion, testing up to 10 equally spaced knots. Model's coefficients were estimated using daily mortality data from January 1, 2011, to December 31, 2019.

Excess mortality was reported in absolute (the difference between observed and expected deaths) and relative terms (as percent deviations from expected mortality) by combining the sex-specific estimates obtained from the regression models. Both measures were computed for all ages and the working-age population, defined as individuals aged between 25 and 64.

We conducted a Monte Carlo simulation to obtain the 95% confidence intervals (CI) surrounding excess deaths. We sampled 10,000 model parameters from a multivariate normal distribution using the parameter's estimates and their variance-covariance matrix. Subsequently, we calculated the variance of the excess death estimates for each simulation by calculating the difference between observed and expected deaths. The 95% CI was then derived using the quantiles of the standard normal distribution.

Statistical analyses were conducted using R software.

3. Results

Table 1 gives the differences between observed and expected deaths in Italy from January to June 2023 for individuals of working ages (25-64 years) and for the whole population. Within the working-age group, we estimated a decrease of approximately 1,800 deaths compared to the expected numbers. This reduction was particularly prominent during the first three months of the year. Similarly, we estimated a decrease of around 8,000 deaths when considering the entire population. This reduction was most notable in March and June.

Figure 1 shows the estimates of excess (or reduced) deaths in absolute and relative terms across four different periods: from March to December the entire 2020, 2021, and 2022, and January to July 2023. Excess mortality for the working-age population stood at approximately +10% in March-December 2020 and 2021, and it decreased to +4.3% in 2022. In January-June 2023, we estimated a reduction of 5.2%. Among the whole population, the excess mortality estimates for March-December 2020 were +18.8%, which decreased to +9.3% in 2021 and +10.2% in 2022. During the first half of 2023, we estimated a reduction in total mortality of 2.1%.

Figure 2 shows the temporal trends of officially reported COVID-19 cases and our estimates of excess mortality in Italy over the pandemic period and up to June 2023. The initial phase, spanning from March to April 2020, showed a sharp increase in excess mortality, even though there were only a limited number of officially registered COVID-19 cases. The subsequent phase, which extended from

Table 1. Difference between observed and expected deaths from all causes in the first six months of 2023 in Italy among the working-age population (25-64 years) and the whole Italian population.

Age group	Month	Observed Deaths	Expected Deaths[1]	Difference	95% CI
Working-age (25-64 years)	January	6,167	6,746	-579	-623 to -534
	February	5,445	5,865	-420	-458 to -381
	March	5,451	6,009	-558	-595 to -520
	April	5,256	5,309	-53	-86 to -19
	May	5,176	5,215	-39	-73 to -4
	June	4,946	5,062	-116	-148 to -83
	Total	**32,441**	**34,209**	**-1,768**	**-1964 to -1571**
All Ages	January	66,607	66,614	-7	-370 to 356
	February	58,311	57,908	403	98 to 707
	March	56,382	59,351	-2,969	-3269 to -2668
	April	52,534	52,468	66	-209 to 341
	May	50,162	51,506	-1,344	-1627 to -1060
	June	46,863	49,942	-3,079	-3340 to -2817
	Total	**330,859**	**337,792**	**-6,933**	**-8404 to -5461**

CI: Confidence Interval.
[1]*Estimated from 2011-2019 mortality and population data, separately by sex, through over-dispersed Poisson regression models including a linear term for the calendar year, age groups as a categorical variable, a smooth function of the day of the year with seven equally spaced knots, and the natural logarithm of the population as an offset term. Values were rounded up to the smallest integer.*

September 2020 to April 2021, was characterized by a complex scenario with multiple waves of COVID-19 cases and important peaks in excess mortality. These peaks were notable but less pronounced than those observed in the first phase. In January 2022, during the Omicron peak, despite a substantial increase in COVID-19 cases, there was no corresponding rise in excess mortality. Later in 2022, different subvariants of Omicron became dominant, leading to new COVID-19 cases and sustained excess mortality. It is worth noting that the mortality peak observed in July 2022 was partially attributed to the extreme temperatures recorded during that month, which was related to an estimate of approximately 12,000 excess deaths. In addition, seasonal influenza peaked in Italy in November-December 2022. The latter part of 2023 displays a significant reduction in both COVID-19 cases and excess mortality.

4. Discussion

We estimated a decrease of over 2% in the total number of deaths in Italy during the first half of 2023 compared to the expected figures based on historical trends. There was also a decrease of over 5% in the working-age population.

The statistical office of the European Union reported that during the first semester of 2023, the entire European Union-27 experienced a level of mortality comparable to or slightly higher than the expected one based on a baseline period spanning from 2016 to 2019 [10]. However, when individual countries are examined, the results are mixed. Some countries, such as Austria and Netherlands, showed important excesses that in some months exceeded 10%, while others, including Bulgaria, Croatia, Lithuania, and Romania, showed decreased mortality.

In England, the Office for Health Improvement & Disparities used a statistical model based on historical trends to derive the expected number of deaths in the absence of the pandemic and found an excess mortality of approximately 18,500 deaths (+6.1%) for the whole population of England in the first six months of 2023 [11]. In the same period, the number of deaths with COVID-19 mentioned on the death certificate was only around 11,500.

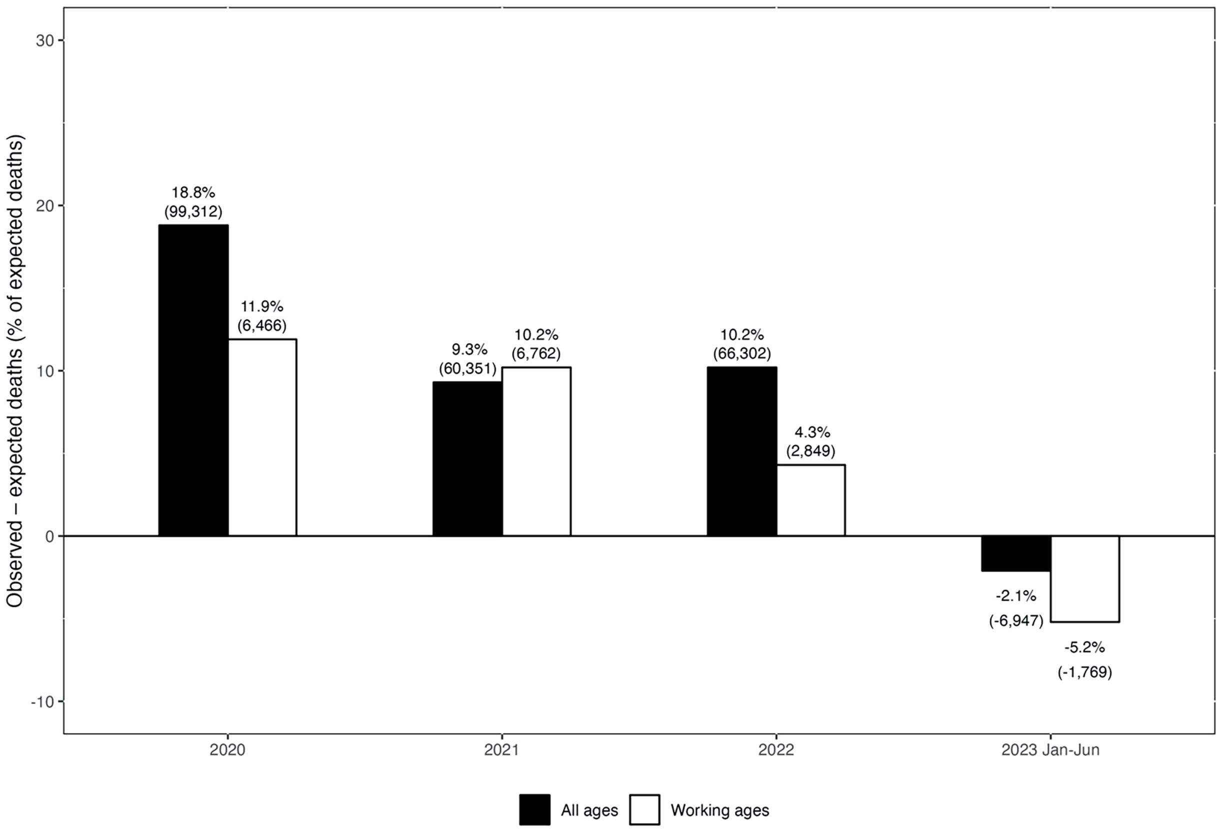


Figure 1. Differences between observed and expected deaths in Italy at all ages and working ages (25-64 years) in March-December 2020, 2021, 2022, and from January to June 2023.

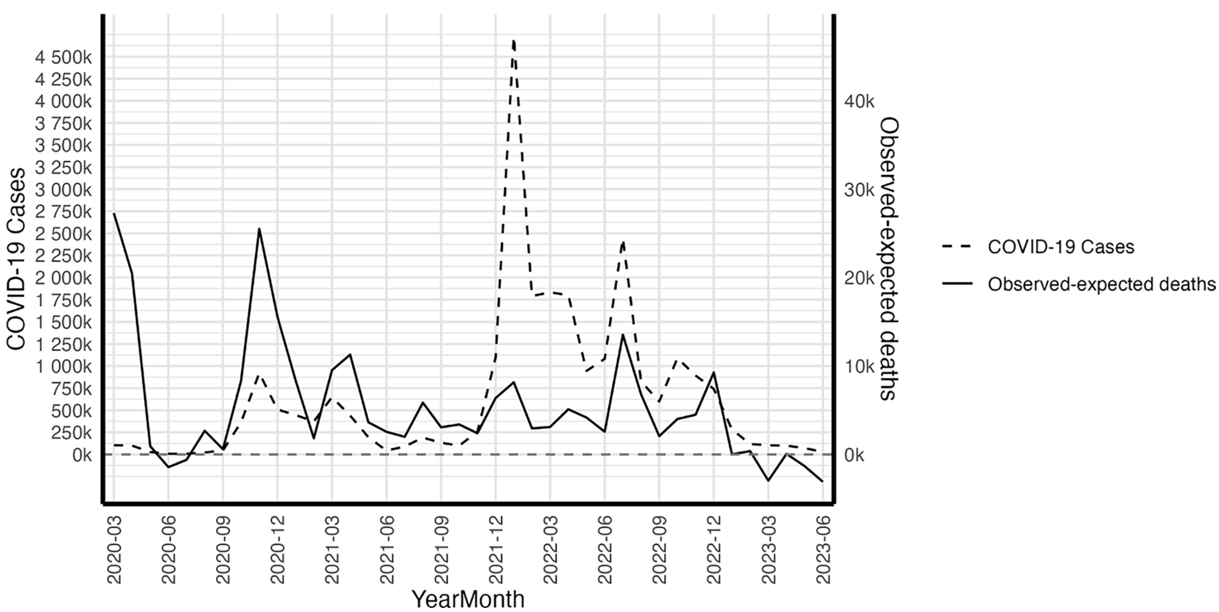


Figure 2. Monthly trend in COVID-19 cases and difference between observed and expected deaths from March 2020 to June 2023 in Italy.

Notably, the excess mortality in England also persisted among the working-age population and was higher than in the older age groups (+12.9% vs. 5.8%) [12]. These excesses were mainly driven by increased mortality from cardiovascular diseases observed in England since the first phase of the pandemic and sustained all over the first semester of 2023.

During the COVID-19 pandemic, mortality from other chronic conditions, including cardiovascular diseases and diabetes, remarkably increased in several countries, including the UK [12]. This increase in excess mortality due to cardiovascular diseases was more pronounced in the younger population than the older one in the UK and several other high-income countries.

The Center for Disease Control and Prevention used a similar model-based approach and reported excess mortality rates of 14%, 9.2%, and 5.2% in the first three weeks of January 2023 for the entire US population, with no significant excesses reported thereafter [13].

Identifying the possible reasons for these differences is challenging, given that countries like Austria, the Netherlands, England, and Italy have all achieved a high level of vaccine uptake and have relaxed non-pharmaceutical interventions implemented during earlier phases of the pandemic. Therefore, structural characteristics of these countries, such as the preparedness and resilience of their health and social care systems in responding to pandemic-induced disruptions, may have played a role.

Variations in the methodology employed to estimate excess mortality, particularly using different baseline periods, should be considered when interpreting our estimates and those provided by other institutions or research groups [14]. Another significant source of differences across countries lies in the provisional data released during the pandemic, along with delayed registration of deaths, both of which can impact cross-country comparisons.

6. Conclusions

Our estimates indicate that during the first half of 2023, there was no excess mortality in Italy, both among the entire population and the working-age population. The modest decrease in mortality during this period can be partly attributed to harvesting and the early arrival of seasonal influenza in the winter of 2022-2023, resulting in a larger impact on mortality in November-December 2022 than in the early months of 2023. While data on total mortality are reassuring for the first half of 2023, the recent increase in COVID-19 cases demands attention. It is crucial for countries to continue providing timely mortality data to effectively monitor the ongoing impact of COVID-19.

Funding: This research was supported by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (project no. PE00000007, INF-ACT).

Declaration of Interest: The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

References

1. Edouard Mathieu, Hannah Ritchie, Lucas Rodés-Guirao, et al. (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' [Online Resource] [Last Accessed October 9, 2023].
2. WHO. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. WHO Dir Gen Speeches 2023:1–6. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic [Online Resource] [Last Accessed October 9, 2023].
3. Australian Bureau of Statistics. Measuring Australia's excess mortality during the COVID-19 pandemic until the first quarter 2023 2023. https://www.abs.gov.au/articles/measuring-australias-excess-mortality-during-covid-19-pandemic-until-first-quarter-2023#cite-window1 [Last Accessed October 9, 2023].
4. Adair T, Houle B, Canudas-Romo V. Effect of the COVID-19 pandemic on life expectancy in Australia, 2020-22. *Int J Epidemiol.* 2023. Doi: https://doi.org/10.1093/IJE/DYAD121
5. Kung S, Hills T, Kearns N, Beasley R. New Zealand's COVID-19 elimination strategy and mortality patterns. *Lancet.* 2023. Doi: https://doi.org/10.1016/s0140-6736(23)01368-5

6. Islam N. "Excess Deaths" Is the Best Metric for Tracking the Pandemic. *BMJ*. 2022;376:o285. Doi: https://doi.org/10.1136/bmj.o285
7. Alicandro G, Gerli AG, Centanni S, Remuzzi G, La Vecchia C. Excess Total Mortality in Italy: An Update to February 2023 with Focus on Working Ages. *Med Lav.* 2023;114:e2023028. Doi: https://doi.org/10.23749/MDL.V114I3.14740.
8. Alicandro G, Gerli AG, Remuzzi G, Centanni S, La Vecchia CL. Updated estimates of excess total mortality in Italy during the circulation of the BA.2 and BA.4-5 Omicron variants: April-July 2022. *Med Lav*. 2022;113: e2022046. Doi: https://doi.org/10.23749/MDL.V113I5.13825
9. Istituto Nazionale di Statistica. Decessi e cause di morte: cosa produce l'Istat 2021: from https://www.istat.it/.https://www.istat.it/it/archivio/240401[Online Resource] [Last Accessed October 9, 2023].
10. Eurostat.2023:1.https://ec.europa.eu/eurostat/databrowser/view/tps00202/default/map?lang=en [Last Accessed October 9, 2023).
11. Excess mortality in England and English regions - GOV.UK n.d. https://www.gov.uk/government/statistics/excess-mortality-in-england-and-english-regions [Last Accessed October 9, 2023].
12. Alicandro G, La Vecchia C, Islam N, Pizzato M. A comprehensive analysis of all-cause and cause-specific excess deaths in 30 countries during 2020 [published online ahead of print, 2023 Sep 8]. *Eur J Epidemiol*. 2023;10/1007/s10654-023-01044-x. Doi: 10.1007/s10654-023-01044-x
13. Hartnett KP, Kite-Powell A, DeVies J, et al. Excess Deaths Associated with COVID-19. MMWR Morb Mortal *Wkly Rep*. 2020; https://ww:826–34. https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm%0Ahttps://doi.org/10.1111/bjh.16785 [Last Accessed October 9, 2023].
14. Levitt M, Zonta F, Ioannidis JPA. Excess death estimates from multiverse analysis in 2009-2021. *Eur J Epidemiol*. 2023:1-11. Doi: https://doi.org/10.1007/S10654-023-00998-2

La Medicina del Lavoro

Case report

Med Lav 2023; 114 (5): e2023041
10.23749/mdl.v114i5.14932

Moldy Hazelnut Husk and Shell-Related Hypersensitivity Pneumonitis: A Possible Novel Occupational Causative Agent

Ozlem Kar Kurt[1*], Neslihan Akanil Fener[2], Erdogan Cetinkaya[3]

[1]Department of Occupational and Environmental Medicine, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Pathology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[3]Department of Pulmonary Medicine, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

Keywords: Hypersensitivity Pneumonitis; Hazelnut Husk and Leaves; Molds

Summary

Hypersensitivity pneumonitis (HP) is a complex immune-mediated interstitial lung disease (ILD) triggered by inhalation exposure to environmental or occupational antigens in genetically susceptible individuals. Novel exposure sources and antigens are frequently identified. However, the causative agent remains unidentified in nearly half of HP cases. Early diagnosis for nonfibrotic-HP and quitting the exposure may prevent the disease progression to fibrotic forms and related complications. Here, we present two cases of HP associated with mold exposure in hazelnut husks, leaves, and shells in hazelnut agriculture.

1. Introduction

Hypersensitivity pneumonitis (HP) is a complex immune-mediated interstitial lung disease (ILD) triggered by inhalation exposure to environmental or occupational antigens in genetically susceptible individuals [1, 2]. In the United States of America, the one-year cumulative incidence rates of HP range from 1.28 to 1.94 per 100,000 people [3]. Novel exposures and antigens have been frequently identified (environment, workplace, hobbies) since the first paper on HP as Campbell published Farmer's Lung in 1932 [1, 4, 5]. However, the causative agent remains unidentified in nearly half of HP cases [1, 2]. Because of the difficulties related to diagnosis and identifying antigen exposure, the final diagnosis of HP requires a multidisciplinary approach that includes pulmonology, radiology, pathology, and occupational-environmental medicine specialists [6, 7]. Turkey is the world's leading producer and exporter of hazelnuts [8]. Italy and Spain are two other important hazelnut-producing countries. But it is seen that all processes in hazelnut farming are more mechanized in other hazelnut-producing countries, unlike Turkey. Hazelnut is an agricultural product grown in Turkey's eastern Black Sea Region. Harvest is usually picked up by non-mechanized way (manually) in this region. After waiting for the drying processes, the nuts are given to the haymaker to separate from the husk. Both these processes are risky regarding mold and dust exposure. This region is also known for the highest rainfall and high

Received 17.06.2023 – Accepted 09.08.2023
*Corresponding Author: Ozlem Kar Kurt: E-mail: okarkurt@gmail.com

humidity levels. Here, we present two cases of HP associated with mold exposure in hazelnut husks, leaves, and shells in hazelnut agriculture.

1.1. Case 1

A 64-year-old nonsmoker woman working as a hazelnut farmer for the last four years presented with progressive dyspnea on exertion, weakness, and fatigue for one year. She described that she had worked in the hazelnut harvest and threshing. She revealed that while hazelnuts wait in the open or closed warehouses to be dried, a strong musty odor and dust from hazelnut husk and leaves occurred and were released into the environment. She had worked with other family members and sometimes helped neighbours while not wearing a mask. In occupational and environmental history, she worked as a cook between the years 2007 to 2017. Based on detailed occupational and environmental history, she had no other relevant exposure history of organic or inorganic dust, birds, or mold-related agents at work and home. She declared that her symptoms worsened while working in hazelnut farming every year from July to September. She had no clinical findings of connective tissue diseases, chronic diseases, or drug usage history. On physical examination, oxygen saturation (SaO_2) was 96% on room air, and basal inspiratory crackles were present on chest auscultation. There was no clubbing.

Her laboratory tests were obtained, including complete blood count, electrolytes, renal and liver function test results, and connective tissue disorders panel. Her fasting blood glucose level was 121 U/L, and others were normal. Rheumatology found no evidence of connective tissue disease.

Pulmonary function tests revealed decreased forced vital capacity (FVC) was 1.19 L (43% predicted); decreased FEV1, 1.13 L (49% expected); FEV1/FVC, 95%. But she was unable to cooperate diffusing capacity of the lung for carbon monoxide (DLCO). A chest high-resolution CT (HRCT) imaging demonstrated diffuse bilateral ground glass patchy opacities, mosaic patterns, and reticulations (Figure 1).

BAL differential count demonstrated 30% lymphocytes, 5% neutrophils, and 65% macrophages.

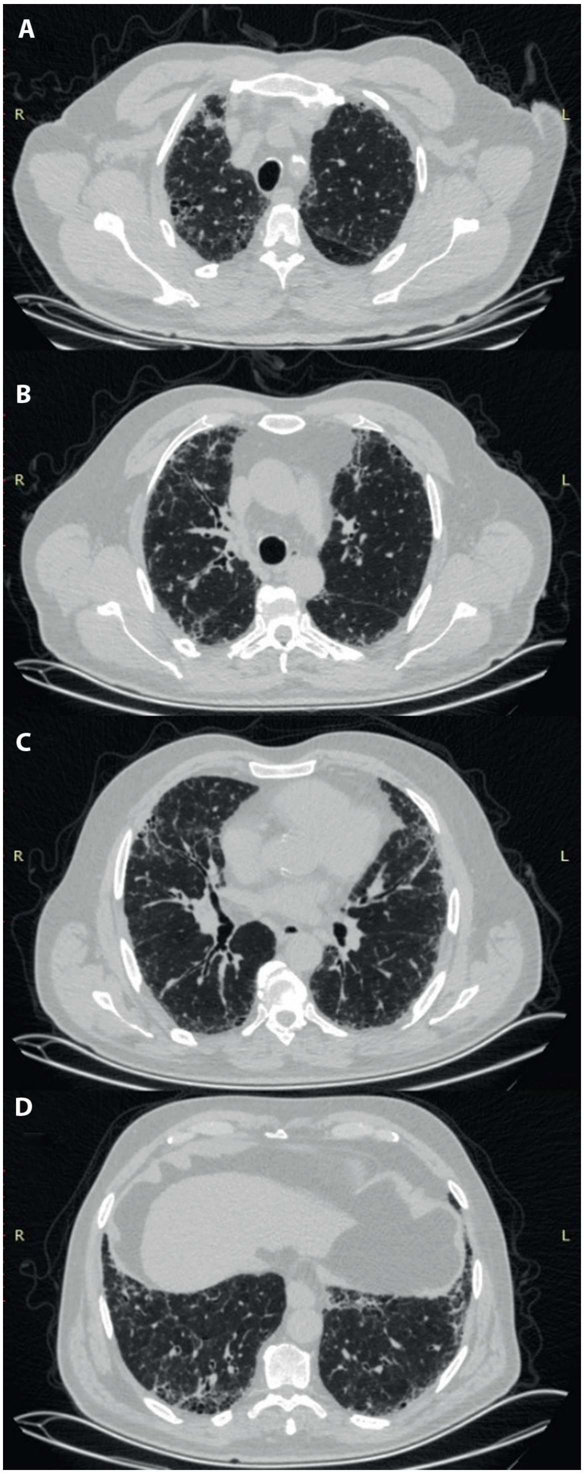


Figure 1. Figure 1A, 1B, 1C, 1D. Chest high-resolution CT imaging of Case 1 showing diffuse bilateral ground glass patchy opacities, mosaic pattern, minimal air-trapping, traction bronchiectasis, minimal honeycombing and reticulations.

The patient underwent a right lung lower lobe transbronchial cryo-biopsy. The pathological examination revealed focal mild interstitial and lymphocytic infiltrates, bronchiolization in alveoli, squamous metaplasia, mucus stasis, fibroblast plugs, and intact alveolar groups in between but without granuloma, which is compatible with HP. The pathological findings were evaluated as probable fibrotic-HP. The final diagnosis of HP related to possible molds contaminating hazelnut storages (husk and leaves) and the environment was decided according to the multidisciplinary discussion (MDD) conducted with the participation of pulmonologists, radiologist, pathologist, and occupational-environmental medicine specialists. Treatment with 0.5 mg/kg/d *p.o.* Prednisone was initiated with gradual tapering, and the patient was instructed to stop occupational exposure.

1.2. Case 2

A 65-year-old male ex-smoker patient was admitted to the hospital with complaints of progressive dyspnea on exertion and cough for two years. He had worked different jobs such as construction worker for one year, textile worker for five years, cleaner for six years, elevator installer for eleven years, and he retired 13 years ago. He also worked hazelnut farming only in the summertime for two months every year from younger ages without using personal protective equipment. The last time he was exposed to molds and dust related to hazelnut farming was the summer before he was admitted to hospital. He revealed that he was dealing with hazelnut harvest and threshing. He had no relevant exposure history of birds or other mold-related environments. The physical assessment results show that he has basal inspiratory crackles on auscultation and clubbing.

Pulmonary function tests revealed that FEV1/FVC: 75%, FVC 2.5 L (106% predicted); FEV 1, 3.19 L (95% expected), with low DLCO such as 57% (22.6), DLCO/VA 75% (4.01), spO2 was 94% mm Hg on room air. HRCT scan demonstrated diffuse bilateral ground glass patchy opacities, mosaic pattern, honeycombing, and interlobular septal thickening. Laboratory tests were normal. Because the BAL differential count was contaminated by bronchial cells (>5%), differential cell analysis could not be performed as it would not represent the diagnosis of ILD. The serological markers of connective tissue disorders were negative. The patient underwent a video-assisted wedge lung biopsy of the left upper lobe revealed poorly formed granuloma structures in the interstitium, subpleural microscopic honeycombing, traction bronchiectasis, fibrosis, lymphoid aggregates in the interstitium (Figure 2).

The pathological findings were evaluated as typical fibrotic HP. A diagnosis of HP related to possible molds contaminating hazelnut storages and environment made. Antifibrotic therapy and 0.5 mg/kg/d *p.o.* Prednisone treatment was initiated with gradual tapering, and she was advised to quit hazelnut farming.

2. Discussion

We demonstrated for the first time an association between molds contaminating hazelnut storages (husk and leaves) and HP in two cases working in hazelnut agriculture without any other related exposures. Only one case reported from Turkey has been collecting green and brown hazelnut leaves to fuel the house, diagnosed as fibrotic-HP [9]. Another study, including workers in a hazelnut processing factory, showed that a significant deterioration in restrictive and obstructive pulmonary functions was observed and concluded the research needs to investigate HP in hazelnut processing [10]. Although metalworking fluid HP and farmers' lungs are the leading occupational subtypes of HP, mold-related working products and processes or environments are being reported with increasing frequency [11, 12]. In hazelnut farming, HP can be related to contaminating molds and plant-derived materials. Pscheidt et al. said that fungi were isolated from kernels with mold and Penicillium spp., species of Aspergillus and Cladosporium, and Diaporthe rudis [13]. As an example of a plant-derived material exposure related to nuts, HP was reported in a worker exposed to dust from a tiger nut in a processing factory (a nut used in the production of horchata, a drink consumed in Spain and Mexico) [14].

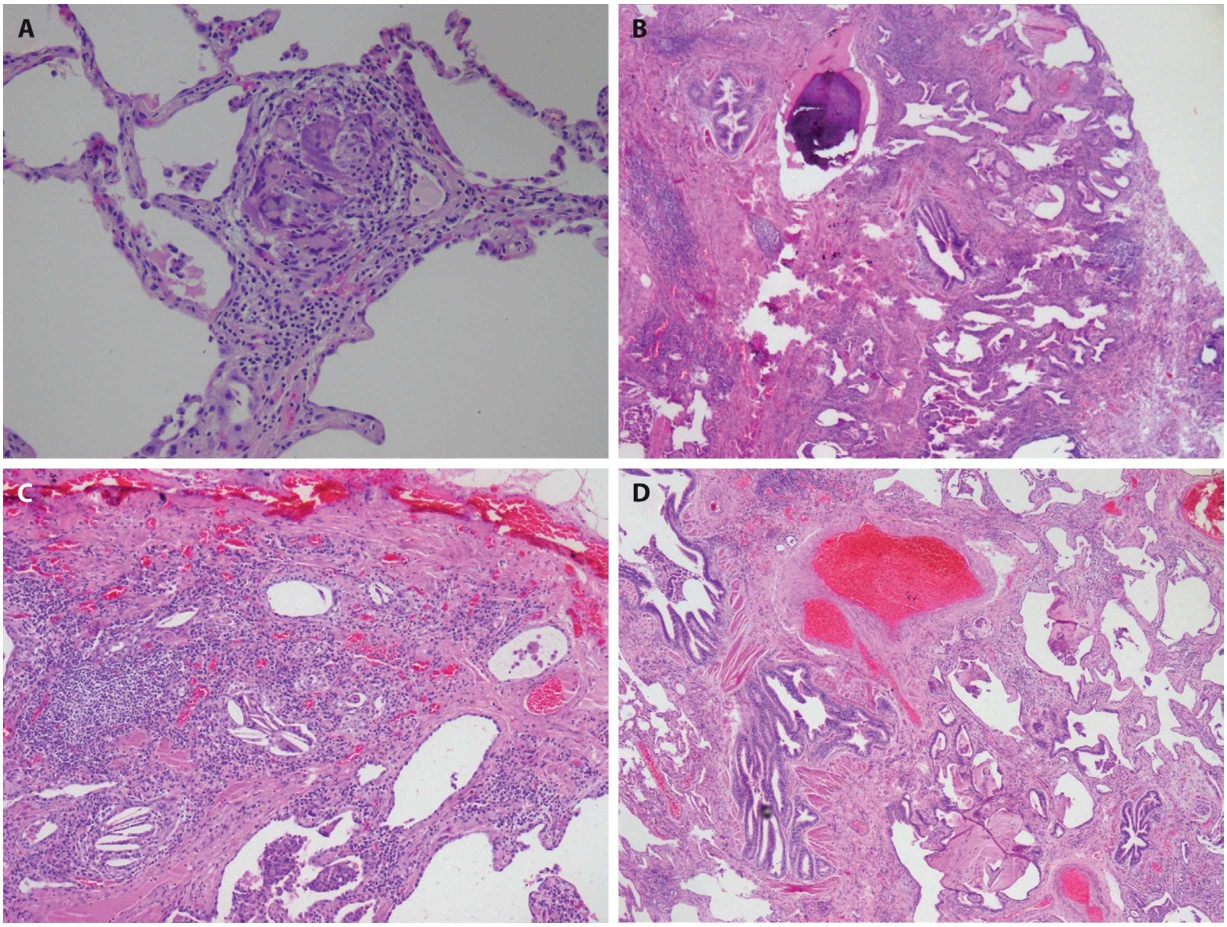


Figure 2. Figure *2*A. Video-assisted wedge lung biopsy of the left upper lobe of Case 2, showing poorly formed granuloma structures in the interstitium (10x10 hematoxylin and eosin), 2B, 2C, 2D displaying subpleural microscopic honeycombing, traction bronchiectasis.

In the first case, the diagnosis of HP was given by transbronchial cryo-biopsy with a BAL fluid lymphocytosis. She had only an exposure history of molds and dust contaminating hazelnut husk and leaves. HRCT findings are compatible with fibrotic-HP. She emphasized that her symptoms were worsening while working in hazelnut farming every year in the summer during the exposure period. A video-assisted lung biopsy of the left upper lobe confirmed the diagnosis of our second patient. He had no exposure to HP besides molds and dust contaminating hazelnut husks and leaves. Both patients declared that an intense musty odor and macroscopically moldy-black or green discoloration appeared on hazelnut husks and leaves due to humid climatic conditions and rain on the threshing. Both patients had fibrotic-HP, so we could not see clinical and radiological improvements after avoiding exposure to hazelnut-related molds.

In our chest diseases hospital, many of the ILD patients are consulted by our occupational and environmental outpatient clinic to identify possible causative agents or exposures that may be related to ILD by interviewing patients face to face with a modified questionnaire and also evaluated in the multidisciplinary discussion (pulmonologists, radiologists, pathologists, and occupational and environmental medicine specialists).

One of the main limitations of our case report is the lack of investigation of the molds for microbiological analyses on the husk and leaves due to the hazelnut harvest not coinciding. Also, the unavailability of specific IgG to standard HP antigens test was one of the critical limitations. So, the findings of these two cases led the authors to investigate either HP in hazelnut farming for microbiological analyses.

In conclusion, we present two cases of HP related to occupational exposure to molds in hazelnut husks, leaves, and shells in hazelnut agriculture. The fact that hazelnut shells are easily molded due to humid climatic conditions and that it is a plant-derived product are possible reasons that increase the risk. Also, less mechanized or manual and traditional systems used in hazelnut farming are a substantial risk for exposure to molds and dust. During the waiting period for the hazelnuts to dry, mold growth is inevitable due to humidity and rainfall. After drying, giving the hazelnuts into the haymaker to separate from the husks is the other primary exposure to dust and molds. People engaged in hazelnut farming in this region do not receive regular occupational health services since they work as a family business in the summer. For this reason, we think it would be beneficial to ensure that employees have access to essential occupational health services, to provide training on the prevention of mold formation in hazelnuts, and to apply mechanized and modern systems.

Early diagnosis for nonfibrotic-HP and quitting the exposure may prevent the disease progression to fibrotic forms and related complications. The findings of two cases led us to investigate HP in hazelnut farming accompanied by case-control or cohort studies.

Declaration of Interests: None to declare.

References

1. Walters GI, Huntley CC. Novel occupational causes of hypersensitivity pneumonitis. *Curr Opin Allergy Clin Immunol*. 2023;23(2):85-91. Doi: 10.1097/aci.0000000000000894
2. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;202(3):e36-e69. Doi: 10.1164/rccm.202005-2032ST
3. Fernández Pérez ER, Kong AM, Raimundo K, Koelsch TL, Kulkarni R, Cole AL. Epidemiology of Hypersensitivity Pneumonitis among an Insured Population in the United States: A Claims-based Cohort Analysis. *Ann Am Thorac Soc*. 2018;15(4):460-469. Doi: 10.1513/AnnalsATS.201704-288OC
4. Kongsupon N, Walters GI, Sadhra SS. Occupational causes of hypersensitivity pneumonitis: a systematic review and compendium. *Occup Med*. 2021;71(6-7): 255-259. Doi: 10.1093/occmed/kqab082
5. Cormier Y, Laviolette M. Farmer's lung. 1993, Thieme Medical Publishers, Inc.; 1993:31-37.
6. Fernández Pérez ER, Travis WD, Lynch DA, et al. Executive Summary: Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. *Chest*. 2021;160(2):595-615. Doi:10.1016/j.chest.2021.03.067
7. Hamblin M, Prosch H, Vašáková M. Diagnosis, course and management of hypersensitivity pneumonitis. *Eur Respir Rev*. 2022;31(163).
8. Castro NR, Swart J. Building a roundtable for a sustainable hazelnut supply chain. *J Clean Prod*. 2017; 168:1398-1412.
9. Erkan F, Baur X, Kiliçaslan Z, et al. [Exogenous allergic alveolitis caused by mouldy hazel nut leaves]. Exogene allergische Alveolitis durch schimmelige Haselnusshüllblätter. *Pneumologie*. 1992;46(1):32-5.
10. Arbak P, Karatas N, Balbay EG, et al. Respiratory symptoms and pulmonary functions in hazelnut workers. *Health Med*. 2011:165.
11. Moran-Mendoza O, Aldhaheri S, Black CJ, Clements-Baker M, Khalil M, Boag A. Mold in Foam Pillows and Mattresses: A Novel Cause of Hypersensitivity Pneumonitis. *Chest*. 2021;160(3):e259-e263.
12. Barnes H, Lu J, Glaspole I, Collard HR, Johannson KA. Exposures and associations with clinical phenotypes in hypersensitivity pneumonitis: a scoping review. *Respir Med*. 2021;184:106444.
13. Pscheidt J, Heckert S, Wiseman M, Jones L. Fungi associated with and influence of moisture on development of kernel mold of hazelnut. *Plant Dis*. 2019; 103(5):922-928.
14. Barranco P, Moreno-Ancillo A, Robles MLM, et al. Hypersensitivity pneumonitis in a worker exposed to tiger nut dust. *J Allergy Clin Immunol*. 1999;104(2):500-501.