

# Current Italian contribution to research in Occupational Medicine

Four centuries ago, science broke his ancestral link with philosophy, adopting Galilei's experimental method. However, still in 1669 Bernardino Ramazzini got his degrees in Medicine and Philosophy, both fields of study belonging to the same metaphysical realm. Medicine did not move to the scientific playground until the second half of the 19th century, when Claude Bernard adopted an experimental approach for his physiological studies, describing rigorous conditions under which any experiment must be reproducible. Despite elapsing time and the tremendous milestones achieved thanks to scientific principles, metaphysic and anti-scientific attitudes and thoughts persist in every field of knowledge, including Medicine. Unfortunately, in Medicine, particularly in Occupational Medicine, our understanding is mostly based on observation of diseases occurring because nature and occupational settings operate in ways that researchers cannot control. Experience, rather than experiments, is the source of knowledge. A collective experience based on individual observations is difficult to build up in a reproducible way. Yet, like other medical disciplines, Occupational Medicine increasingly needs to found professional practice on a solid scientific ground that guarantees evidence and appropriateness for its varied activities.

Three types of issues need to be considered in the application of epidemiology results to individuals. First, epidemiology results are subject to random error. They can be applied only to an ideal subject with average values of all variables under study, such as potential confounders included in the regression models. Second, epidemiology's observational nature makes it susceptible to systematic error, and any extrapolation to individuals would mirror the validity of the initial results. Quantitative bias analysis has been proposed to assess the likelihood, direction, and magnitude of bias, but this has not yet become part of epidemiology's practice. Finally, the external validity of results (i.e., their application to individuals and populations other than those included in the underlying studies) needs to be addressed, including population-based factors, such as heterogeneity in exposure or disease circumstances, and individual-based factors, such as the interaction of the risk factors of interest with other determinants of the disease. Similar considerations are valid also to the application of clinical trials results to individual patients, although in these studies, sources of systematic error are better controlled (1).

Over the last few decades, several groups and associations tried to set up a framework to share criteria to extract and review knowledge from epidemiological studies. Systematic Reviews have been introduced to improve the synthesis of available evidence and reduce bias in the conclusions about a body of evidence. Nowadays, Systematic Review is an established method also in the Occupational Safety and Health (OSH) field. The Cochrane Work Review Group facilitates authors to produce Cochrane reviews of intervention topics in this area. A variety of guidelines used Cochrane Work reviews for underpinning their recommendations. Due to the reproducibility of the comprehensive search of systematic reviews, it turned out that such an approach can be powerful in changing beliefs. For example, studies published in the eighties advocated the use of back schools. Nowadays, we know that the total body of evidence has changed the traditional view that lifting techniques could prevent back pain. 'Sitting is the new smoking' is an eye-catching nicely alliterating motto, but it is of course highly overstated. The findings of a Cochrane review of the effects of interventions to decrease sitting at work showed that sitting time can be reduced by a bit less than two hours per day by providing sit-stand desks plus education. However, it is unclear if this is sufficient to counter the effects of sitting. A wealth of evidence on OSH interventions has been collected by international collaboration in the Cochrane Work Review Group (2).

Guidance tools for occupational physicians and, in particular, the Guidelines of Scientific Societies represent an indispensable contribution to correct professional practice. In many countries, National Societies of

Occupational Medicine, regularly publish policy tools and guidelines for the occupational physician. It is not always possible to base the Guidelines in occupational Medicine exclusively on consolidated scientific evidence. However, it is still necessary to increase research and publications aimed at evaluating the effectiveness of specific interventions in the preventive, clinical and rehabilitative field of occupational Medicine to guide occupational physicians to an increasingly appropriate practice. In Italy, a recent law allows the production of Guidelines that partially exempt criminal liability for inexperience through a System of Guidelines produced by accredited Scientific Societies (3).

Neither a cause nor a risk factor is recognised for many chronic diseases labelled as “idiopathic”, though occupational hazards are thought to play a role. One such condition is idiopathic pulmonary fibrosis (IPF), a rare lung disease of unknown origin that rapidly leads to death. The disease progression rate varies from one individual to another and is still difficult to predict, though its prognosis is poor, with a median survival of three to five years after diagnosis, without curative therapies other than lung transplantation. The factors leading to disease onset and progression are not yet completely known. The current disease paradigm is that sustained alveolar epithelial micro-injury caused by environmental triggers (e.g., cigarette smoke, particulate dust, viral infections or lung microbial composition) leads to alveolar damage resulting in fibrosis in genetically susceptible individuals. Numerous epidemiological studies and case reports have shown that occupational factors contribute to the risk of developing IPF. In this perspective, the current understanding of the pathophysiology of IPF and the importance of occupational factors in the pathogenesis and prognosis of the disease was reviewed to identify and eliminate occult exposure, which may represent a novel treatment approach in patients with IPF (4).

Various techniques to monitor lung function are available to address the old problem of exposure to free crystalline silica, which is emerging unexpectedly in work settings where the risk of exposure is overlooked. The reliability of spirometry compared to body plethysmography in detecting restrictive lung disease was assessed in clay excavation workers exposed to free crystalline silica. Only one out of 14 cases of restrictive deficit diagnosed based on total body plethysmography values was also identified using spirometry. This finding supports the need to use body plethysmography in the health surveillance of workers exposed to free crystalline silica and perhaps other restrictive lung diseases (5).

Functional tests and traditional diagnostic tests are complemented by molecular and epigenetic markers providing mechanistic insights on work-related non-communicable diseases. However, their use is still limited to research projects. Non-communicable diseases (NCDs) are chronic diseases that are by far the leading cause of death globally. Together with social, economic, and demographic factors, many occupational hazards have been associated with NCDs development. Genetic susceptibility or environmental exposures alone are not usually sufficient to explain the pathogenesis of NCDs. Still, they can be integrated into a more complex scenario that can result in pathological phenotypes. Epigenetics is a crucial component of this scenario. Its changes are related to specific exposures, potentially displaying the effects of the environment on the genome, filling the gap between the genetic asset and environment in explaining disease development. To date, the most promising biomarkers have been assessed in occupational cohorts and case/control studies. They include DNA methylation, histone modifications, microRNA expression, extracellular vesicles, telomere length, and mitochondrial alterations (6).

The gradual worldwide expansion of industrialisation has led to a dramatic increase in the production and use of chemical substances, resulting in a greater dispersion of these pollutants in the environment and an increased exposure of the general population and workers. In this new scenario, a thorough knowledge of exposure levels is needed to assess chemical risks in environmental and occupational settings. Biological monitoring is among the most useful tools for assessing exposure. However, to provide adequate guidance in implementing risk management measures, biomonitoring results need to be compared with appropriate references. Reference values (RVs) provide useful information for a correct interpretation of toxicological data, by comparing them with biomonitoring results. In Public Health, this may enable us to identify potential sources of exposure, define the principal and most frequently exploited routes of exposure, and outline chemical absorption. Similarly, in Occupational Medicine, RVs can be used to give meaning to biomonitoring

findings, especially when a biological limit value is not available for the chemical in question. Furthermore, these values are a tool for classifying as occupational any otherwise environmental exposure to chemical carcinogens. Therefore, by integrating reference values in an appropriate and complete system of guide values that includes action levels and biological limit values, we could obtain an adequate assessment of exposure and a better understanding of toxicological data (7).

The realisation that work will continue to change in the future requires that the field of occupational safety and health include but go beyond traditional concerns such as exposures to chemical, physical and biological agents and focus on an expanded paradigm that addresses the interaction occupational and individual risk factors, the work-life continuum and ultimately on operationalising and implementing a concept for the well-being of workers. This holistic view will require new systems thinking and transdisciplinary approaches to occupational safety and health in the future (8).

Criteria for diagnosis and compensation of occupational musculoskeletal diseases varies widely between countries as demonstrated by the large differences among countries with comparable economic and social systems (for example, within the European Union). Several countries have a list of occupational diseases, and sometimes these lists include diagnostic and attribution criteria. Still, these criteria are usually not very specific, and they may also be very different. Their use may improve the process of diagnosis and attribution of an occupational musculoskeletal disease. It makes it possible to associate a probability rank to the attribution and, ultimately, improve the overall quality of the occupational physician's decisional process (9).

Psychosocial risk management represents a current challenge in Occupational Health and Safety (OSH) due to their impacts of such risks on work stress and the rapid changes of the world of work. Effective psychosocial risk management can be carried out based on an integrated multidisciplinary model founded on the risk management paradigm. Over the years, Occupational Medicine has played an essential role in creating an integrated and participatory approach. Emerging risks have to be tackled by translating the knowledge obtained from research into policies that have a driving role in identifying and implementing actions and practical tools (10).

Personalised medicine “relies on identifying individual variability in genomic, biological, and physiological parameters, integrating them with environmental and lifestyle factors for designing “individually” targeted disease prevention and treatment. Although innovative “omic” technologies supported the application of personalised Medicine in clinical, oncological, and pharmacological settings, its roles in occupational health practice and research are still in a developing phase. Occupational personalised approaches have been currently applied in experimental settings and in conditions of unpredictable risks, e.g., war missions and space flights, where it is essential to avoid disease manifestations and therapy failure. However, a debate is necessary regarding whether personalised Medicine is even more critical to support a redefinition of the risk assessment processes considering the complex interaction between occupational and individual factors. Indeed, “omic” techniques can help understand the xenobiotics' hazardous properties, dose-response relationships through a more in-depth elucidation of the exposure-disease pathways and internal doses of exposure. Overall, this may guide the adoption/implementation of primary preventive measures protective for the vast majority of the population, including most susceptible subgroups. However, personalised Medicine into occupational health requires overcoming some practical, ethical, legal, economic, and socio-political issues, particularly concerning privacy protection and the risk of discrimination that the workers may experience. In this scenario, the concerted action of academic, industry, governmental, and stakeholder representatives should be encouraged to improve research aimed to guide effective and sustainable implementation of personalised Medicine in occupational health fields (11).

Occupational Medicine is more and more concerned with Public Health issues and is actively involved in prevention programmes. In our journal, two emerging issues have been dealt with by the SIML Scientific Committee: tuberculosis (TB) and the COVID-19 pandemics.

For decades, tuberculosis (TB) control programmes have focused almost exclusively on infectious TB active cases. However, this strategy alone cannot achieve TB elimination. It has recently been recognised that latent TB infection (LTBI) is not a stable condition but rather a spectrum of infections (e.g., intermittent,

transient or progressive), which may lead to incipient, then subclinical, and finally active TB disease. LTBI diagnostic test is not available to directly identify live MT infection in humans. The diagnosis of LTBI is indirect and relies on detecting an immune response against MT antigens, assuming that the immune response has developed after contact with the biological agent. Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are the main diagnostic tools for LTBI; however, both present strengths and limitations. The most ancient diagnostic test (TST) can give rise to several technical errors, has limited positive predictive value, is being influenced by BCG vaccination, and several conditions can reduce the skin reactivity.

Nevertheless, a TST conversion should orientate indications for preventive therapy of LTBI. IGRAs have superior specificity, are not affected by *M. Bovis*, BCG vaccination and other environmental mycobacteria. However, they present some logistical and organisational constraints and are more expensive. Early identification and treatment of individuals with LTBI is an essential priority for TB control in specific groups at risk within the population: this is crucial in recently infected cases both at the community level and in some occupational settings. An improved understanding of the available tests is needed to develop better tools for diagnosing LTBI and predicting progression to clinically active disease (12).

Over the last year, a dozen papers dealing with COVID-19 have been published by our journal, covering various aspects of the pandemics. Most articles were calling for a broader scope of Occupational Medicine to include the disease's multifaceted issues, starting from diagnostic problems covered by an official document of the Italian Society of Occupational Medicine (13) to problems associated with smart working and programmes aimed at primary and secondary prevention. New problems arise when people who suffer from the disease should obtain a fitness certificate for job reintegration, which can only be issued by a multidisciplinary team, including an occupational physician. The importance of being interconnected with other disciplines sharing a concern with prevention is an essential lesson of COVID-19 (14).

All the articles summarized in this short overview have been published in the section "Advances in Occupational Medicine research", which for two years opened each new issue of *La Medicina del Lavoro | Work, Environment & Health*. We thank the members of the Scientific Committee of the Italian Society of Occupational Medicine (SIML) for their valuable contribution, feeding the SIML-sponsored continuing education programme and providing an updated account of recent advances in the different branches of our discipline. They will collaborate again with our journal in a new section, which will be entitled "Commentaries, Perspectives, Insights" to show a broader scope and to include what is still under development but is likely to affect the future of Occupational and Environmental Health. The first article of this series provides an excellent example of this kind of contributions (15).

Two additional changes are being introduced in our journal: our scientific articles will be published in English only, and our Publisher will ensure free open access to all papers, which starting from the vol. 109 (2018) are now available not only from our site (Mattioli Health) but also from Pub Med Central (PMC). Although both such changes are mainly aimed at disseminating Italian research, they furtherly open the journal to contributions coming from other countries and international agencies.

**Antonio Mutti**

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## 83° Congresso Nazionale della Società Italiana di Medicina del Lavoro (Parma, 15-17 settembre 2021)

### TEMI DEL CONGRESSO

- Impatto dell'innovazione tecnologica e dell'impresa 4.0 sulla Medicina del Lavoro
- Contributo della Medicina del Lavoro alle valutazioni di impatto sanitario degli insediamenti industriali
- COVID-19 e mondo del lavoro
- Medicina del Lavoro P4 (Predittiva, Preventiva, Personalizzata e Partecipativa)
- Invecchiamento della popolazione attiva e medicina di genere: nuovi indicatori biologici e vecchi problemi interpretativi

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