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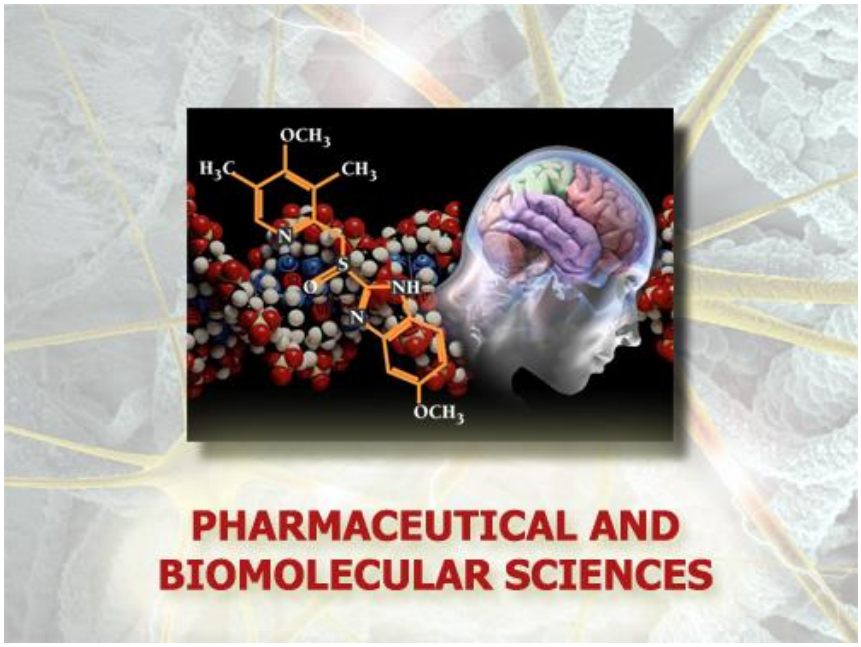

Biological evaluation of quality of life: analysis of the inflammatory profile and oxidative and biomolecular status in population studies.

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Biological evaluation of quality of life: analysis of the inflammatory profile and oxidative and biomolecular status in population studies.

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Next [after the goddess Metis] he [Zeus] married bright Themis who bare the Horai (Horae, Hours), and Eunomia (Order), Dike (Justice), and blooming Eirene (Irene, Peace), who mind the works of mortal men, and the Moirai (Moirae, Fates) to whom wise Zeus gave the greatest honour, Klotho (Clotho), and Lakhesis (Lachesis), and Atropos (Atropus) who give mortal men evil and good to have.

Hesiod, "*Theogony*" 901 ff (Greek epic C8th or 7th B.C.)

Already he was a very different hobbit from the one that had run out without a pocket-handkerchief from Bag-End long ago. He had not had a pocket-handkerchief for ages.

J.R.R. Tolkien (1937), "The Hobbit"

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My endless gratitude and love to my family, for everything (and more).

To the curious little girl I was, who did not know what to do when she grew up.

Abstract

Introduction

Despite the concept of Quality of Life (QoL) being pretty self-explanatory, its operationalisation is quite recent and dates back to the 90s. Until then, the health-related measurements were unable to evaluate the perception of life (and health) *through the eye of the experiencer*, *i.e.* mediated by cognitive factors and cultural settings, and thus relying more on the experience than on the objective life conditions. The possibility to combine the individual's perceptions to biomarkers used as a proxy of the various processes involved in the stress response and, in the broadest sense, to life experiences, is not only fascinating, but it could provide some interesting insights useful from the perspective of health promotion.

Aim

The aim of the present study is to analyse the possible relationship between bio-molecular measurement and QoL evaluations to provide useful tools for an objective assessment and promotion of QoL in different populations.

Methods

To make an attempt to investigate this relationship, we performed a systematic review of the literature focused on the working environment and we implemented three experimental study lines. The subjects enrolled in these studies were workers (study lines 1 and 2) and pregnant women (study line 3): indeed, we supposed that the pathways involved in the relationship between the peculiar stressors of each group and the QoL could be similar, highlighting the broad spectrum of scenarios where these links are worth to be investigated.

Aiming to actively promote health and well-being, in two study lines (1 and 3), we implemented a web-based exercise training intervention and we observed how this program might eventually result in a re-balance of QoL and the bio-molecular profile.

Discussion

In conclusion, based on the results obtained, we observed that having a valid array of indicators, biological and self-reported, sensitive to both the derangements from physiological conditions and their restoration due to stress reduction would be desirable and worth to be investigated in further studies.

1. Introduction

1.1. Quality of Life

1.1.1. History and definition

The core concept of Quality of Life (QoL) and its importance have accompanied the history of mankind. It could be identified over time in the thoughts of philosophers such as Aristotle ("*All the people perceive the concept of living in good or being well, that is the same of being happy*", *Ethica Nichomachea*), and in political projects, such as in the conceptualisation of the Great Society by the XXXVI US president Lyndon B. Johnson to promote the economic growth and the social programs enhancement following the World War II, with a focus on community development, health, and welfare ("*Our basic task is threefold: First, to keep our economy growing; to open for all Americans the opportunity that is now enjoyed by most Americans; and to improve the quality of life for all*", *Excerpts from President Lyndon B. Johnson's State of the Union Address January 4, 1965*) (Megari 2013; Mandzuk and McMillan 2005). The QoL has been so far considered a key element in many different fields, such as education, family contexts, healthcare availability, and interaction with the anthropic environments (Mandzuk and McMillan 2005).

The operationalization of the QoL concept in its current form, however, is a quite recent achievement. Until then, the traditional assessment of health at both individual and population levels was focused merely on indicators, such as morbidity and mortality, or evaluations of the impact of diseases and impairments on daily life (WHOQOL GROUP 1994). In the last decades, the rise of a holistic approach in addressing the topic of health made necessary the introduction of a humanistic element, described as a "*missing measure in health care*" (WHOQOL GROUP 1994). This dimension, based on individual perceptions, is naturally connected with the cultural settings of respondents. One of the biggest challenges in its conceptualisation was, indeed, ensuring the ability to perform cross-cultural comparisons of epidemiological data (WHOQOL GROUP 1994).

According to the World Health Organisation (WHO), QoL can be described as the "*individual's perception of their position in life in the context of the culture and the value systems in which they live and in relation to their goals, expectations, standards, and concerns"*. The main characteristic of this concept is thus its multidimensionality, encompassing the individual's physical health, psychological status, level of independence, social relationships, personal beliefs, and relationships to salient features of the environment (WHOQOL GROUP 1994). The QoL formalisation, as consequence, implies awarding a value to an extensive range of human experiences, states, perceptions, and spheres of thought (Patrick and Erickson 1993). The result is thus an assessment performed *through the eye of the experiencer,* mediated by cognitive factors and relying more on the experience than on objective life conditions (Ziller 1974; Ferrans et al. 2005; Megari 2013).

The identification of the objective measurements most suitable to supplement these subjective evaluations could be really useful to obtain an even more comprehensive evaluation and characterisation of the health status at the population level and in identifying subjects deserving specific interventions (Megari 2013).

1.1.2. Quality of Life and Health

In health care, researchers focus their attention on the Health-Related QoL (HRQoL), which was defined by the Center for Disease Control (CDC) as "*an individual's or group's perceived physical and mental health over time*" (Taylor 2000). This evaluation is more strictly focused on the impact of dysfunctions, disabilities, injuries, and health behaviours (Shockey, Zack, and Sussell 2017).

These evaluations become particularly useful in the management of chronic disorders, characterised by a slow progression but lasting over the years and possibly requiring life-long medical treatments with various intensities (Mandzuk and McMillan 2005). Indeed, evaluating the patients' appraisal of their current functioning level and their degree of satisfaction with it could be particularly useful in identifying the most suitable treatment choice, aiming to improve patients' QoL (Shockey, Zack, and Sussell 2017; Megari 2013). At the population level, this indicator has been associated with various health outcomes, socio-demographic and environmental features (Shockey, Zack, and Sussell 2017). This information, as part of the health surveillance evaluations, could represent a key element not only in the definition of public health policies, but also in related fields, such as healthcare economics, psychology, sociology, environmental sustainability, and urban planning (Shockey, Zack, and Sussell 2017).

Non-communicable diseases (NCDs) are often chronic conditions linked to chronic stress and to the adoption of health risk behaviours, and are becoming increasingly prevalent worldwide (Suvarna et al. 2020). Lifetime strain is a fundamental problem associated with daily life in today's society (Suvarna et al. 2020). The awareness that the stressors could exert a cumulative physiological "wear and tear" throughout the lifespan has encouraged researchers to evaluate the role of chronic stress in such widespread detrimental effects on health (Suvarna et al. 2020).

1.2. Physio-pathological mechanisms

1.2.1. Allostatic load

"*The social and physical environments 'get under the skin' and shape the brain and the body*"
(McEwen 2017)

Losses in the perception of QoL and well-being, however, may likely precede, follow or be independent of eventual diseases (Edimansyah et al. 2007).

The fundamental feature of life is the energy flow. At the molecular level, this phenomenon sustains chemical reactions, movements, and dynamic changes in molecules, resulting in our ability to sense, feel, think, move, and behave (Picard et al. 2018). More in general, in the consciousness through which we perceive the world and in how we face reality (Picard et al. 2018; Bobba-Alves, Juster, and Picard 2022). As consequence, eventual deficits in the available energy to power life-sustaining cellular and physiological activities can variously affect the individual health status and contribute to the onset of subclinical, at first, and then clinical alterations until full-blown disease states (Picard, Wallace, and Burelle 2016).

Environmental conditions may be often changing and sometimes stressful, triggering the alteration of physiological systems stability (Robertson et al. 2015). The stress response is a complex process characterised by the activation of several interacting mechanisms, including behavioural, autonomic, endocrine, and immune systems, occurring whenever there is a discrepancy between expectation and reality (Harris et al. 2007; Ghelli et al. 2022). Although this process leads to an adaptive response, the sustained activation of these pathways can trigger physiological and behavioural alterations which, in the long run, may result detrimental to survival and well-being (Herman 2013; Ghelli et al. 2022). Indeed, alongside the capacity to directly face sudden and unexpected challenges, living organisms evolved the ability to anticipate internal and environmental perturbations and to perform adaptive physiological recalibrations to minimise deviations, in a process called allostasis (Bobba-Alves, Juster, and Picard 2022). The basis of this concept is the paradox that the neuroendocrine, autonomic, metabolic, and immune mediators involved in adaptation are the same involved in the onset of pathophysiological consequences when dysregulated (McEwen 2006; Picard et al. 2018). In physiological conditions, they are turned on in a

balanced way to overcome challenges and then turned off again (Picard et al. 2018). Allostasis is thus that process that allows the maintenance of constant physiological parameters throughout the changes in other parameters by a controlled release of a host of mediators in a coordinated and energy-dependent manner (Picard et al. 2018). The implementation of this large spectrum of energy-consuming compensatory modification, either functional or structural, when chronic, induces a "domino effect" on interconnected biological systems, overcompensating and eventually collapsing themselves, in a stress-disease cascade (Juster, McEwen, and Lupien 2010; Bobba-Alves, Juster, and Picard 2022). Moreover, systemic signals can interact at the cellular level with age, genes, and the epigenome responsible for past-experiences registration (Picard et al. 2018). The dysregulation consists of "*moving the goal posts*", *i.e.*, on the physiological operating set points or on the mechanisms involved in the adaptation and restriction to these conditions (Bobba-Alves, Juster, and Picard 2022; Robertson et al. 2015). The triggering of these transitory allostatic responses could be due to either real or imagined stressors in order to cope with challenges and promote survival (Bobba-Alves, Juster, and Picard 2022). The alteration of physiological regulatory set-points and/or dynamic range leads to the transition to the allostatic state, which can assume different forms, such as repeated activation, lack of habituation, prolonged response, and inadequate response (McEwen and Stellar 1993). Sustaining these processes over time represents an additional energetic cost leading to eventual more lasting maladaptive recalibrations, such as hyperglycemia, elevated blood lipids, and elevated circulating stress mediators (cortisol, catecholamines, etc). This can result, in turn, in the organ systems "wearing out", in a condition called allostatic load (McEwen and Stellar 1993). Common consequences are the arteries stiffening to sustain high blood pressure, the hormone receptors downregulation on target tissues to counteract overstimulation, and the brain circuitry and anatomy remodeling in response to neurochemical factors (Bobba-Alves, Juster, and Picard 2022). The stimulation persistence over time and the absence of restoration to physiological conditions lead to a breakdown in communications and regulatory systems known as allostatic overload. At the molecular level, this condition is characterised by molecular changes, such as damage accumulations and accelerated aging, culminating in the onset and progression of diseases, and, ultimately, in premature death (Bobba-Alves, Juster, and Picard 2022). Importantly, this stress-disease cascade progressing from adaptive allostasis to maladaptive allostatic states and allostatic load, and, finally, to allostatic overload activates the progressive "wear and tear" and the consequent derangements from the physiological condition in terms of physical and mental health, predisposing the disease onset.

There is, however, an extremely huge inter-individual variability in body conditions, with metabolic imbalances increasing the vulnerability to stress, and in how different individuals could respond to potentially stressful situations, essentially based on how the situation is perceived and interpreted (McEwen 2006). The perception of threats and the triggering of the allostatic mechanisms are fundamentally shaped by individual differences in constitutional (genetics, development, experience), behavioural (coping and health habits), and historical (trauma/abuse, major life events, stressful environments) factors, determining the individual resistance to stress (Juster, McEwen, and Lupien 2010).

There is still no consensus concerning the definition of "stress", with some authors proposing to restrict the definition to those unpredictable and uncontrollable conditions in which the environmental demands exceed the natural regulatory capacity of an organism, and others sustaining the need to distinguish positive and negative stress conditions (Picard et al. 2018). Moreover, the term is often used in relation to the damage or dysfunction resulting from challenges, overuse, or exposure to toxins (Picard et al. 2018).

Stress states are not necessarily harmful, but the duration of the condition, quality, magnitude, subjective appraisal, and context can shape the stress response (Agorastos and Chrousos 2022). In this last perspective, there could be identified three classes of stress: good,

tolerable, and toxic. The first, also called "*eustress*", arises from the chance to achieve a goal: in this situation primary mediators such as cortisol and adrenalin are turned on strictly for the duration of the challenge (to promote adaptation) and then turned off again. Tolerable stress is related to bad events, but the experiencer has personal resources and a support system making him/her able to face the situation and be resilient. In this situation the chronic or repeated activation of mediators may turn into pathophysiological processes, leading to cardiovascular, immune, and metabolic dysregulation and to changes in the brain circuits involved in emotion regulation. However, the worsening of this condition and the onset of long-term consequences can be limited by individual resources and external support, minimising the effects and eventually promoting a resolution. When these positive features are not available, chronic dysregulation can lead to pathophysiological consequences promoting the development of disorders, either physical or mental (Picard et al. 2018). However, there is not a linear relationship between physiological mediators and linear outcomes, and the temporal dimension from the primary stress mediator alterations to the onset of clinical outcomes remains still unclear (Suvarna et al. 2020).

From an energetic perspective, the need to reduce to a minimum the energy expenditure led to the evolution of likes and dislikes, feelings and emotions, and approach/withdrawal behaviors (Damasio 2019). Human beings tend, indeed, to like those things that give or allow them to save energy (e.g., palatable food and warm clothes, respectively), and dislike what lead to an extra-energy expenditure (e.g., cold rain) to minimize physiological perturbations (Sterling 1990).

The original definition of allostatic load by McEwan and Stellar assume a cumulative effect of past experiences, both ordinary events as well major challenges (McEwen and Stellar 1993; Fava et al. 2022). The analyses of psychobiological responses to daily-life stressors in order to understand the mechanisms leading to psychological, physical and behavioural disorders is currently a fertile research field (Giessing et al. 2020; Ghelli et al. 2022). Different levels in allostatic load are consistently associated with several factors, including age, sex, gender, socioeconomic status (SES), income inequalities, adverse living conditions, adverse experiences in childhood, living in impoverished neighbourhoods, education, social relationship, work and unemployment, lifestyle, race/ethnic, and genetic factors (Fava et al. 2022; Juster, McEwen, and Lupien 2010; Juster and Lupien 2012). Specific protective factors have thus far being identified throughout the lifespan development, such as parental bonding, education, social support, healthy workplaces, and purpose (Juster, McEwen, and Lupien 2010). While it is now clear that the maladaptation to stressful environment could lead to serious consequences, the continuous exploration of risk and protective factors influencing this phenomenon is nowadays imperative in a health promotion perspective (Juster, McEwen, and Lupien 2010). The implementation of health promotion programs targeting the antecedents of allostatic load is therefore of uttermost importance to promote life-long resilience and health (Juster, McEwen, and Lupien 2010). Indeed, if prevention can pre-empt the negative effect of stress, the implementation of interventions can effectively minimise the onset of health outcomes, resulting in improving the health status even in case of early warning signs or biological signatures (Beckie 2012).

1.2.2. Risk behaviours

Allostatic load can also be the consequence of common unhealthy lifestyles and health-damaging behaviours, such as (i) an unhealthy diet high in fat, sugar, and sodium but low in important nutrients intake (e.g., trans–fatty acids) and mostly relying on foods with a high glycaemic index (Armborst et al. 2018), (ii) a sedentary life with very little physical activity, (iii) smoking, (iv) substance abuse, such as alcohol and illicit drugs , (v) inadequate sleep, and (vi) social isolation (Suvarna et al. 2020; Picard et al. 2018).

"Risk behaviours" have been indeed defined as "*behaviours that increase the likelihood of adverse physical, social, or psychological consequences*" (Carr-Gregg, Enderby, and Grover 2003). The relationship between allostatic load and risk behaviours is interchangeable, with these last being often a coping mechanism to relieve with negative emotions and mental issues such as stress, depression, and anxiety, exacerbating the allostatic load (Suvarna et al. 2020). The three-part definition of stress shed up light on the importance of control and mindset in determining the positive or negative outcome of the stress response and the behaviour subsequently adopted (McEwen 2017). "*Stressed out*" individuals, indeed, may feel anxious or depressed, lose sleep at night, eat comfort foods (resulting in the intake of unnecessary calories), smoke and drink alcohol excessively, neglect social relationships, take time off from work, reduce engagement in physical activity, and take medications to cope with the situation, resulting in developing symptoms of the unhealthy lifestyle (McEwen 2017). The relationship between allostatic load, health risk behaviours and mental health is an emerging topic gaining ever more attention, especially in exploring potential beneficial role of health enhancing behaviours in reducing the allostatic load and, in turn, in reducing the subsequent disease burden (Suvarna et al. 2020). The implementation of these knowledge can be achieved at different levels. The major goals should be creating motivating contexts at home and in working settings and in encouraging educational programs sensitising people to adopt healthy lifestyles, such as improving sleep quality and quantity, improving social support, and promoting a positive outlook of life, maintaining a healthy diet, avoid smoking and excessive alcohol consumption, and have a regular physical activity (McEwen 2017). The challenge, thus, is to find ways to redirect future behaviours and physiology in a healthier direction, promoting a full enjoyment of life at the same time reducing the financial burden on individuals and society (McEwen 2017).

1.2.3. Oxidative stress

Oxidative stress was defined for the first time by Helmut Sies in 1985 as "*an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage*" (Sies 1985). This phenomenon is the consequence of an enhanced generation of Reactive Oxygen Species (ROS) or Reactive Nitrosative Species (RNS) and/or a reduction in the antioxidant protective ability turning into a reduced capacity of endogenous systems to counterbalance the oxidative attack directed towards target biomolecules (Pisoschi and Pop 2015). Basically, at the cellular level, a steady-state redox balance is maintained, and eventual departures are considered a stress, initiating a stress response (Sies 2020).

Oxidative stress and its severeness are associated with several pathophysiological outcomes (Pisoschi and Pop 2015). The damage induced by the free radical attack to biomolecules was indeed confirmed as a contributor in over 100 diseases, such as neurodegenerative conditions (Parkinson, Alzheimer, Huntington's disease, and amyotrophic lateral sclerosis), emphysema, cardiovascular and inflammatory diseases, cataracts and cancer (Pisoschi and Pop 2015). This pathway was also involved in the ageing process, especially in the decay of physiological functions, the rise of disease incidence, and the subsequent reduction in lifespan (Pisoschi and Pop 2015).

Free radicals are reactive chemicals with an unpaired electron in an outer orbit capable of independent existence and that can be produced in aerobic processes such as cellular respiration or as a consequence of the exposure to microbial infections, extensive exercise, or pollutants/toxins such as cigarette smoke, alcohol, ionizing and UV radiations, pesticides, and ozone (Poljsak, Šuput, and Milisav 2013). Since the exposure to ROS is ubiquitous, a basal oxidative damage level is thus present in any individual (Graille et al. 2020). In mitochondria, the cellular respiration employs oxygen to oxidize biomolecules containing carbon and hydrogen to produce chemical energy and heat; during this process, molecular oxygen is stepwise reduced to a series of intermediate ROS:

hydroperoxyl radical, superoxide radical anion, hydrogen peroxide, hydroxyl anion and hydroxyl radical (Pisoschi and Pop 2015). To counteract the damaging effects of these highly-reactive species, aerobic organisms developed an antioxidant network consisting of antioxidant enzymes (such as superoxide dismutase, catalase, glutathione peroxidases) and endogenous low-molecular-mass antioxidants (*e.g.*, glutathione, ubiquinol, bilirubin, uric acid, α-tocopherol, and ascorbic acid) (Sies 2020).

The balance between the ROS production and the antioxidant defence result in the ROS constitutive levels, at both tissue and systemic level. Such differences can be due to differences in ROS generation intensity and in the antioxidant defence effectiveness (Il'yasova, Scarbrough, and Spasojevic 2012). Intra- and inter- individual variability in oxidative status are a result of a complex interaction among multiple factors, including genetic and epigenetic differences, endogenous promoters of ROS (such as iron and copper), chronic inflammation or other chronic conditions (Il'yasova, Scarbrough, and Spasojevic 2012).

At cellular level, ROS can cause the oxidation of lipids containing carbon-carbon double bonds in membrane lipid bilayers (Mas-Bargues et al. 2021). These reactions lead to the production of highly reactive molecules such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which can play a role of toxic messengers spreading and magnifying the oxidative damage (Mas-Bargues et al. 2021). Research on oxidative stress and lipid peroxidation are currently topical (due to its close association with disease onset and aging) and engaging multidisciplinary professionals, such as analytical chemists, physicians, pharmacologists and toxicologists, sport medicine specialists, and nutritionists (Tsikas 2017). Oxidative stress and inflammation are interdependent mechanisms able to trigger each other (Biswas 2016), representing a further molecular pathway through which chronic stress can lead to health worsening. Chronic and sub-chronic psychological stress has been associated with lipid peroxidation, oxidative DNA damage, hydrogen peroxide, and superoxide dismutase activity (Casado et al. 2008; Takaki 2013).

1.2.4. Inflammation

Inflammation is a comprehensive set of physiological processes that an organism undertakes in response to a foreign stimulus, including pathogens, such as viruses and bacteria, and inorganic particles (Ferrero-Miliani et al. 2007).

Furthermore, inflammation is also the basic process by which the tissues of the body respond to injury. Celsus (I AC) was the first to describe the four clinical signs of inflammation: *calor*, *dolor*, *rubor*, and *tumor*. Galen, subsequently, added the *function laesa*. The presence of these five cardinal signs can be traced back, at molecular level, to the effects of chemokines, cytokines, and other inflammatory mediators on local blood vessels and tissues, leading to vasodilatation and increased permeability (resulting in the changes in temperature, redness, and swelling), to the migration of cells into tissues and to the stimulation the nerve endings (leading to pain and swelling) (Romero et al. 2007).

The inflammation starts when the body senses a "danger": the exposure to pathogen-associated molecular patterns and damage-associated molecular patterns leads to the activation of pro-inflammatory genes, to the suppression the anti-inflammatory ones, and in the regulation of cytokines, chemokines and other chemicals production, resulting, in turn, in the modulation of non-specific cellular recruitment and humorally-mediated vascular changes (Bennett et al. 2018). Non-antigenic stimuli may as well be perceived as a "danger", leading to the inflammatory response activation, as in case of radiation, ischaemia, toxin exposure, and psychological stress (Bennett et al. 2018). These factors may lead to the activation of the inflammatory response by means of the ativation of neuroendocrine pathways (e.g., emotional stress), through the upregulation of stress

response pathways (e.g., ischemic stroke), or by the induction of P450 pathway and the dysregulation in oxidative balance (e.g., environmental toxins and chemicals) (Bennett et al. 2018).

Depending on the duration of these processes, it is possible to distinguish between two inflammatory response types: acute and chronic (Arulselvan et al. 2016). In both cases, a key role is played by cytokines, protein-based chemical mediators produced by a broad range of cells, including the immune cells recruited in the inflammation site. These polypeptides are pleiotropic molecules that elicit their effects in an autocrine or paracrine manner, binding to specific receptors on cell walls and regulating their activation (Feghali and Wright 1997).

Chronic inflammation, instead, can occur in either an asymptomatic or symptomatic way. A chronic inflammatory state is the hallmark of several metabolic conditions and plays a key role in the pathophysiology and in the progression of several disorders, such as metabolic syndrome, type 2 diabetes, stroke, and cardiovascular disease, altered neuronal functions, increased risk of mood and cognitive decline, neurodegenerative processes during ageing, neuronal health impairment and neuronal loss (Devoto et al. 2017). The maintenance of high circulating inflammatory cytokine levels and/or the sustained activation of the stress system can result in immune and metabolic disturbances, leading, in turn, to an increase in morbidity and all-cause mortality (Elenkov et al. 2005; Ghelli et al. 2022).

1.2.5. Neuro-endocrinal activation

Stress can trigger the activation of both the sympathetic-adrenal-medullary (SAM), resulting in autonomic nervous system regulation (e.g., heart rate), and the hypothalamus-pituitary-adrenal (HPA) axes, leading to the release of glucocorticoids such as cortisol (Armborst et al. 2018). Salivary α-amylase has been proposed as a biomarker of the SAM activation and short-term stress, being positively correlated with norepinephrine and (nor)adrenaline levels (Feicht et al. 2013). The abnormal activation of the SAM axis, as in the case of sleep deprivation, could lead to increased heart rate and blood pressure, activation of the renin-angiotensin system, and trigger oxidative stress and inflammation (Mullington et al. 2009). Simultaneously, the sustained and repeated HPA axis activation can lead to excessive production of cortisol and, in turn, to physiological and psycho-neuro-endocrinological alterations and to health issues such as hypertension, insulin resistance, hyperglycaemia, inflammation, visceral fat accumulation, and metabolic syndrome (Armborst et al. 2018). The different patterns resulting in the HPA axis activation have been also related to neuropsychiatric disorders, such as, for example, an increase in cortisol production in subjects affected by major depression, often associated with cognitive impairment (Sandstrom et al. 2011). Cortisol has a particular circadian rhythm, characterised by a peak just before awakening followed by a gradual decline during the day. Hyper- and hypo-activation of this system have been associated with several health outcomes; for example, a high awakening cortisol response has been related to depressive symptoms, while an attenuated response was reported in subjects affected by burnout (Harris et al. 2007; Iglesias et al. 2015; Ghelli et al. 2022).

1.3. Measuring the Bio-molecular Profile

1.3.1. Biomarkers

The WHO defined a biomarker as "*any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*" (Frijhoff et al. 2015). In clinical practice, a useful biomarker must: (i) have a diagnostic value, i.e., be specific for a certain disease, (ii) have prognostic value, (iii) correlate with disease manifestations, (iv) be

reasonably stable, (v) be measurable in tissues easily accessible, and (vi) be cost-effective making possible to be reproducibly assessable on a large scale (Frijhoff et al. 2015).

The ultimate goal of investigations in molecular epidemiology field is to provide reliable and specific information on the etiology and mechanisms of disease to define effective strategies for disease prevention (Bonassi and Au 2002). In this perspective, the identification of biomarkers related to the onset of pathophysiological consequences before the occurrence of any symptoms related to a full-blown disease in order to surrogate the disease incidence is a very appealing approach (Bonassi and Au 2002).

The huge inter-individual variability which can affect these measurements represents a valuable element in enhancing the possibility to identify and customise sustainable and effective preventive measures addressing the subjects or groups at higher risk (Bonassi and Au 2002).

The identification of a valid array of subclinical biomarkers sensitive to the physiological consequences of chronic stress can provide interesting insights into a person's health and well-being (Chandola and Zhang 2018), and could be combined with self-reported measures to obtain an overall assessment.

1.3.1.1. Early Biological Effect Biomarkers

1.3.1.1.1. Oxidative status

The growing literature confirming the role of oxidative stress in several pathophysiological processes rely on the measurements of biomarkers employed as a proxy of this phenomenon. Indeed, the direct ROS quantification remains difficult, since some have a short life and do not accumulate enough to be measured (Graille et al. 2020). Moreover, since ROS production take place even in physiological condition and many of the biomarker investigated did not have a threshold discriminating "normal" form "altered" situations, it is rather preferable to generally refer to the individual "*oxidative status*" (Il'yasova, Scarbrough, and Spasojevic 2012). Eventual alterations in those biomarkers able to display an alteration in the oxidative status, could be influenced by the adoption of unhealthy lifestyles and behaviours and to the exposure to environmental and/or occupational agents (Graille et al. 2020).

1.3.1.1.1.1. 15-F2t-Isoprostane

The lipid oxidation generates hydroperoxides, which are subsequently fragmented resulting in a wide range of relatively stable endproducts, such as prostaglandin F2α isomer F2-IsoPs (Graille et al. 2020). After being released into the blood stream by phospholipases, F2-IsoPs are rapidly metabolized in the liver, and then excreted as free acids in urine (Graille et al. 2020).

Specifically, the free radical-induced peroxidation of arachidonic acid independently of the cyclooxygenase (COX) lead to the productions of IsoPs, prostaglandin-like molecules generated *in vivo* in humans (Milne, Dai, and Roberts 2015).

The addition of an oxygen molecule to the arachidonic acid lead to the production of 4 different regioisomers, according to the position where oxygen is added. Each regioisomer is at the base of a F2-isoprostane series, each one comprising four stereoisomers (Il'yasova, Scarbrough, and Spasojevic 2012).

The quantification of F2-isoprostanes can be performed in human blood and urine, both in the general and in pathological populations. In urine, these molecules are chemically stable and their concentrations is not affected by the lipid dietary intake. The high inter-individual variability combined to a small intra-individual variability make these molecules particularly suitable biomarkers for epidemiological investigations (Il'yasova, Scarbrough, and Spasojevic 2012). More

specifically, the 8-iso-prostaglandin F2α (also known as 15-F2t-IsoP) was identified through coordinated experimental studies led by the National Institute of Environmental Health Sciences as the most useful biomarker for the assessment of the oxidative damage and has been thus the most commonly measured F2- isoprostane to date (Shoman et al. 2020; van 't Erve et al. 2017). This molecule is a potent vasoconstrictor and is able to modulate platelet activity, inhibit angiogenesis, and promote atherosclerosis by stimulating adhesion of monocytes and neutrophils to endothelial cells (Milne, Dai, and Roberts 2015). High levels of these molecules have been associated with a variety of health conditions and environmental exposures, such as pregnancy, obesity, ischemia-reperfusion injury, disorders affecting the central nervous system, cancer, genetic disorders, pathologies involving the kidneys and lungs (van 't Erve et al. 2017; Milne, Dai, and Roberts 2015). Some studies, howewer, highlight, as potential limitations of this study, the presence of an alternative enzymatic pathway leading to the production of this molecule by prostaglandin endoperoxide synthase, making diffucult to identificate which pathway is involved in the generation of the biomarkers quantified in biological specimens (van 't Erve et al. 2017).

1.3.1.1.1.2. Thiobarbituric Reactive Substances

Malondialdehyde (MDA), as well, is a well-studied end-product of the lipid peroxidation detectable in plasma, urine or tissues and largely investigated as a biomarker of oxidative stress (Toto et al. 2022; Turcu et al. 2022). MDA is a biologically active compound involved in insulin secretion and collagen-gene expression in hepatic cells, that can be generated through both a non-enzymatic and an enzymatic pathway (Toto et al. 2022; Ping et al. 2009). In this last case, it can be regarded as a biomarker of lipid peroxidation, and high concentrations were found to be associated with many health issues, such as cardiovascular disease, diabetes, Alzheimer's, DNA damage, ageing, cancer, psychiatry, chronic obstructive pulmonary disease, asthma, or cardiovascular diseases, autoimmune diseases, such as lupus erythematosus, nephritis, and atherosclerosis (Turcu et al. 2022; Hardt et al. 2018; Khoubnasabjafari, Ansarin, and Jouyban 2015). MDA has also been employed as biomarkers of early biological effects in pulmonary oxidative stress and in evaluating the impact of air pollution, smoking, or respiratory exposure in occupational environments, to investigate the effects of the exposure to nanoparticles and heavy metals (Turcu et al. 2022; Bergamaschi et al. 2022). The reactivity of the two aldehyde groups of these molecules towards nucleophiles enables MDA to form adducts with other biomolecules, such as proteins, amino groups, and DNA, resulting in genotoxic effects (Toto et al. 2022; Bono et al. 2016). The ability to form adducts has been used to the implementation of the TBARS assay is a commonly used method for the detection of lipid peroxidation, where thiobarbituric acid may be used to detect MDA-TBA2 by production of a pink-colored product (Mas-Bargues et al. 2021).

1.3.1.1.1.3. Total Antioxidant Power

Antioxidant are defined as "*any compound that, when present at a lower concentration compared to that of an oxidizable substrate, is able to either delay or prevent the oxidation of the substrate*". (Pisoschi and Pop 2015). Antioxidant are thus involved in several functions, implying lowering oxidative stress, DNA mutations, malignant transformations, as well as other parameters of cell damage (Pisoschi and Pop 2015).

The redox homeostasis is guaranteed by the endogenous antioxidant defense system, which includes endogenous antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase), and non-enzymatic compounds like glutathione, proteins (ferritin, transferrin, ceruloplasmin, and even albumin) and low molecular weight scavengers, like uric acid, Coenzyme Q, and lipoic acid (Pisoschi and Pop 2015).

1.3.1.1.2. Inflammatory Status

The immune system can be considered as made of two branches, working in concert to most efficiently remove harmful antigens from the body. Whereas the innate immune system is a first line of defense responsible for the enhancement of the inflammatory response, the adaptive branch is designed to "learn" and create "memory" of the exposures experiencesd across the lifespan (Bennett et al. 2018). Cytokines can be classified according to their role as pro-inflammatory, anti-inflammatory, or chemotactic. The pro-inflammatory cytokines owe their name to their role in orchestrating the early immune response to infection/injury by recruiting immune cells to the infection site and activating them (Wieseler-frank, Maier, and Watkins 2005). They are often released in a cascade, and the lack of control over their release/activity can lead to damage to host tissues as well as pathogens (Wieseler-frank, Maier, and Watkins 2005). The main cytokines with a pro-inflammatory role are interleukin (IL)-1β, IL-6, and tumour necrosis factor α (TNF-α). Anti-inflammatory cytokines, instead, such as IL-4 and IL-10, play a crucial role in controlling the regulation of pro-inflammatory cytokines. Finally, chemokines are a cytokine subgroup whose main role is the activation and recruitment of leukocytes, as, for instance, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1a, MIP-1b and IL-8 (Zhang and An 2007). Another non-cytokine polypeptide, named C-reactive protein (CRP), is an acute inflammatory protein that increases its concentration at sites of inflammation or infection (Sproston and Ashworth 2018). It may be considered a useful diagnostic tool in the assessment of early inflammation, such as in acute-phase diseases (Ziemowit Zietkowski et al. 2010). Most biomarkers of inflammation and oxidative stress (OS) are often investigated in clinical settings using invasive biological matrices, such as blood and broncho-alveolar lavage (Ghelli et al. 2022).

1.3.1.1.2.1. Interleukin 6

IL-6 is involved in the mediation of both acute and chronic inflammation, where it plays a key role in accumulation of mononuclear cell at the injury site, through continuous MCP-1 secretion, angioproliferation and anti-apoptotic functions on T cells (Gabay 2006). However, IL-6 can have also a protective effect in acute responses, suppressing the level of pro-inflammatory cytokines, and stimulating the production of the IL-1 receptor antagonist, an anti-inflammatory mediator (Gabay 2006).

1.3.1.1.2.2. Interleukin 10

IL-10 is a key anti-inflammatory cytokine fundamental in processes such as wound healing, autoimmunity, cancer, and homeostasis, ensuring the protection of the host from eccessive responses (Saraiva, Vieira, and Garra 2019). The robust immune suppressive response in macrophages and other Antigen Presenting Cells (APCs) was performed mainly *via* the transcriptional inhibition of cytokines, chemokines, and costimulatory and adhesion molecules (Saraiva, Vieira, and Garra 2019). IL-10 also limits the induction of nitric oxide synthase and the production of nitric oxide, as well as the release of reactive oxygen intermediates (Saraiva, Vieira, and Garra 2019).

1.3.1.1.2.3. Interleukin 8

IL-8 is released by several cell types (monocytes, lymphocytes, granulocytes, fibroblasts, endothelial cells, epithelial cells, hepatocytes, mesangial cells and chondrocytes) in inflammatory conditions (Matsushima, Yang, and Oppenheim 2022). IL-8, is involved in the acute inflammation

regulation through the recruitment of neutrophils and the neutrophils egression from bone marrow into the peripheral circulation (Matsushima, Yang, and Oppenheim 2022). Circulating IL-8 levels are elevated and high levels of IL 8 is detected in injured tissues of these inflammatory diseases (Matsushima, Yang, and Oppenheim 2022).

1.3.1.1.2.4. MCP-1

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is involved in the regulation of the recruitment and infiltration of monocytes/macrophage necessaire for the tissue immunological surveillance and in response to inflammation (Deshmane et al. 2009).
MCP-1 is also involved in the insulin resistance development, and was reported to be elevated in patients with gestational diabetes mellitus in the third trimester compared to healthy pregnant women (Klein et al. 2008).

1.4. Scenarios where to perform measurements

1.4.1. Working Environment

1.4.1.1. Special Focus: Burnout and Work-Related Factors

The burnout is a psychological work-related stress syndrome, emerging as a prolonged response to chronic interpersonal stressors on the job, and occurring when there is an imbalance between too high job demands and scarce job resources, such as individual autonomy, social support and feedback receiving (Moraes, Hitora, and Verardi 2019; Maslach and Leiter 2016).

This disequilibrium, defined as a "*state of vital exhaustion*", results in negative feelings that have been classified in three dimensions: (i) an overwhelming exhaustion, (ii) feelings of cynicism and detachment from the job (depersonalisation), and (iii) a sense of ineffectiveness and lack of accomplishment (Maslach and Leiter 2016).

This condition generally affects individuals having assigned a high value to their working activity, and the expression "*to be burned-out*" is used to describe their no longer ability to "*burn*", *i.e.*, to be productive concerning their responsibilities (Ochentel, Humphrey, and Pfeifer 2018). The research performed in the last decades identified several organizational risk factors playing a role in the burnout onset, such as workload, control, reward, community, fairness, and values (Maslach and Leiter 2016). The long-lasting exposure to high job demands lead to the sustained activation of psychophysiological systems over long periods, and burnout is one of the side-effects of this derangement from physiological conditions (Vries and Bakker 2022).

A more recent definition refers to burnout as a state of "*physical and psychological exhaustion due to prolonged exposure to work-related problems*". Indeed, exhaustion, *i.e.*, the feeling of being emotionally depleted and in the limit of all the possibilities, has long been considered the core symptom of burnout, resulting in loss of enthusiasm for work, feeling helpless, trapped, and defeated (Moraes, Hitora, and Verardi 2019; Shoman, Rousson, and Bianchi 2022; Romani and Ashkar 2014).

This condition can affect individuals performing all type of jobs, but was found to be especially common among those professionals working extensively assisting other individuals and seeking the meaning of their job through a recognition from the population and the institution where they work (Moraes, Hitora, and Verardi 2019). Several studies reported a high prevalence of burnout worldwide, especially among physicians, nursing staff and healthcare providers, even higher after the recent COVID-19 pandemic. In a study from the United States, 45.8% of physicians reported having at least one symptom of burnout, with the highest frequency among those

operating at the front line of care access, such as in emergency medicine, general internal medicine, and family medicine (Shanafelt et al. 2012). As well, the study by the European General Practice Research Network Burnout Study Group performed in 2008 across twelve European countries, revealed that the 43% of respondents scored high for emotional exhaustion (Soler et al. 2008).

To date, occupational burnout has not been recognised yet as a medical condition. The lack of a nosological characterisation and of an official diagnosis limits the access to treatment, disability coverage, and workplace accommodations for individuals experiencing this condition (Shoman, Rousson, and Bianchi 2022; Maslach and Leiter 2016). As consequence, it could be inaccurately or incorrectly diagnosed and treated, reducing the possibilities for a successful recovery (Maslach and Leiter 2016a). Given the high prevalence of this phenomenon, the investigation of burnout is thus of uttermost importance, in order to prevent the related negative effects (Monsalve-reyes et al. 2018).

The burnout syndrome can significantly affect workers' health, and is associated with long-term medically certified absences, independently of mental or physical comorbidities (Ahola et al. 2008). The most frequent symptoms reported by individuals suffering from this condition is an excessive, persistent or even chronic physical as well as mental fatigue, which is a known risk factor for several other diseases, like acute myocardial infarction, heart disease, common colds, flu, gastrointestinal disorders, and infections (Ochentel, Humphrey, and Pfeifer 2018). Exhaustion have been also associated with stress symptoms as headaches, gastrointestinal disorders, muscle tension, hypertension, and sleep disturbances (Maslach and Leiter 2016). Burnout may thus be a risk factor for diseases such as cardiovascular disease, metabolic syndrome and depression, resulting in a further weakening of the individuals already suffering from this condition and intensifying the state of exhaustion (Ochentel, Humphrey, and Pfeifer 2018). Indeed, a one-unit increase in burnout score was reported to be associated to a 1.4 unit increase in risk for hospital admission for mental health problems, as well as a one-unit increase in risk for hospital admissions for cardiovascular problems (Maslach and Leiter 2016).

Burnout can thus result in a reduction of individuals' QoL. The extensive workload, including night periods, strong rhythm, requests for increased productivity, leaves only a few moments to leisure activities, rest, personal care or physical exercise (Moraes, Hitora, and Verardi 2019). Since high burnout scores were even reported to be strongly associated with the (ab)use of alcohol, tobacco and psychotropic medication (Soler et al. 2008), the promotion of a healthy lifestyle through the adoption of healthy habits such as a healthy diet, alcohol consumption reduction, relaxation and mindfulness therapies, physical activity, creative activities, spiritual and/or religious practices, and spending time with friends etc. is highly recommended (Ochentel, Humphrey, and Pfeifer 2018).

Since the majority of burned-out workers keep performing their activities and may suffer for long-lasting cognitive impairments even in the non-clinical burnout stage, the prevention of this condition is fundamental (Shoman, Rousson, and Bianchi 2022; Kirsi Ahola, Toppinen-tanner, and Seppänen 2017). Indeed, it would result in improving the workers' health, QoL and job performance, avoiding the threaten of potentially serious consequences, and, more in general, to a cost reduction in terms of both healthcare and working life (Shoman, Rousson, and Bianchi 2022; K Ahola et al. 2009). According to some recent esteems, burnout is responsible of a huge economic burden for the society, estimated in 136.4 billion dollars in U.S. and 200 billion euros in Europe (Naczenski et al. 2017).

1.4.2. Living Environment

1.4.2.1. Special Focus: Pregnancy

1.4.2.1.1. Quality of Life modulation during pregnancy

Pregnancy is a period characterised by several biochemical, physiological, psychological, and anatomical transformations. These changes are beyond the individual's control and could result in an increased vulnerability, exacerbated by the hormonal change impact on emotional regulations, the reduced ability to carry out usual responsibilities, and the concern about the fetus (Boutib et al. 2022). These changes are also associated with transient common issues (*e.g.*, morning sickness, low back pain, movement restriction, Pelvic Girdle Pain and sleep disorders), which, even not representing a serious threat for health, may play a role in reducing pregnant women QoL (Kazemi, Dadkhah, and Torabi 2022).

In a recent systematic review Boutib and colleagues identificated the following factors as able to influence, in either positive or negative way, the pregnant women QoL (Boutib et al. 2022):

- *Factors associated with a QoL decrease: Adolescent motherhood, advanced maternal age, high parity women, low educational level, the perception of fiscal situation, physical changes causing limitations, physical activity limitations, fear of managing labor, the preparedness for parenthood, place of receiving prenatal care, inadequate antenatal care consultations and living in a poor household, partner satisfaction, poor sleep quality, headache or migraine, anxiety and depression, fear of COVID-19, adherence to behavioral restrictions, the perception of health condition, higher overall gestational weight gain, gestational diabetes mellitus, the severity of nausea and vomiting, heart burn and regurgitation, low back pain, urinary incontinence, pathological pregnancies and hospitalization were factors frequently indicating a poor QoL during pregnancy.*
- *Factors associtated with a QoL increase: Exercise, moderate physical activity in water, high exercise adherence, adopting low-to-moderate intensity resistance training, Higher Energy Expenditures, clinical pilates exercises, having a body mass index BMI ≥ 25, better sleep quality, increase of sexual satisfaction, receiving a lifestyle advice, social support and receiving the solution-focused counselling in terms of violence.*
- *Factors appearently not associated with a variation in QoL: planned pregnancies and history of depression were not associated with low mental or physical QoL, and offering an exercise program during pregnancy does not seem to influence healthy pregnant women's psychological wellbeing and self-perceived general health* (Boutib et al. 2022).

During pregnancy, the QoL was commonly reported to increase from the 1st to the 2nd trimester, and then to decrease in the 2nd and 3rd trimesters. Particularly, during the last month of pregnancy women reported a lower perceived health status than at the 3rd month. However, other studies reported no variation in QoL (Boutib et al. 2022).

The eventual reduction in the QoL scores, especially in the physical and social domains, could be due to typical issues such as arising from weight gain, pain and fatigue, as a consequence of the greater load on the musculoskeletal system, even more problematic in women with higher pre-gestational or gestational BMI (Nascimento et al. 2011).

1.4.2.1.2. Bio-molecular Profile alteration during pregnancy

In pregnancy, the modulation of the inflammatory and oxidative status is fundamental to ensure the maintenance of both maternal and fetal health.

Indeed, a derangement from physiological conditions in terms of inflammation can represent a risk for detrimental consequences, such as disruptions in immune function, vascular physiology, endocrine activity, and fetal development, and may be related to the onset of negative outcomes such as preeclampsia, preterm birth, and fetal growth restriction (Mor et al. 2011).

Since alterations in these pathways can be tributed to non-genetic factors, these pathways are currently investigated also to analyse the relationship between environmental exposures and pregnancy outcomes (Welch et al. 2022).

During pregnancy, the development of the fetus' tissues and organs require oxygen consumption and is related to the generation of ROS in both maternal and fetal tissues, which, in turn, can affect the replication, differentiation, and maturation of the developing cells (Toboła-Wróbel et al. 2020).

The main source of these reactive molecules is the placenta, whose cells are particularly rich in mitochondria. Consequently, a dysregulation in the balance between ROS and antioxidants can lead to complications and impairments in fetal development, until early pregnancy loss (Hussain et al. 2021; Duhig, Chappell, and Shennan 2016). A significant rise in the ROS production is typical of the second trimester, due to the enhancement in metabolism, and a rise in the consumption/utilisation rate of oxygen and fatty acids. During the third trimester, instead, the increase in insulin resistance, fat catabolism, and release of free fatty acids lead to a higher production of H_2O_2 (Hussain et al. 2021). On the other hand, the total antioxidant capacity is low in the first phases of pregnancy, and tend to increase during the second and third trimesters, reaching similar levels than in in non-pregnant women (Hussain et al. 2021).

The different stages of pregnancy are characterised by distinct immunological profiles due to immunological changes at the fetal-parental interface, resulting in a unique condition whose modulation is involved in the protection of both the mother and the fetus (Goudreau et al. 2021). Indeed, the enhanced maternal immune system is alerted and more effective in recognition, communication, trafficking, and repair (Mor et al. 2011). On the other side, the fetus developing immune system can modulate the mother's one, modulating how it can respond to environmental stimuli. Contrary to what has long been considered, in pregnant women the immune system is not suppressed, but is active, functional, and carefully controlled (Mor et al. 2011).

During pregnancy there is a shift from a non-specific innate over the acquired and antigen specific adaptive immune system (Ravi, Bernabe, and Michopoulos 2022).The first stages of the pregnancy, from the implantation to the early phases of the second trimester, are characterised by a strong pro-inflammatory response, to cope with the uterus tissues remodelling to secure the implantation and the adequate placental-fetal blood supply, in a scenario that was described as "*a veritable battleground of invading cells, dying cells, and repairing cells*" (Mor et al. 2011). The mothers' body attempt to adapt, combined with the simoultaneous hormonal changes, is responsible to the sickness feelings, typical of this period (Ravi, Bernabe, and Michopoulos 2022). The subsequent phase, characterised by a rapid fetal growth, is an optimal time for the mother, with a symbiontic relationship between mother, placenta and fetus. From the immunological perspective, it is characterised by an anti-inflammatory state. Finally, after the completing development of the fetus, the last immunological stage is characterised by a renewed inflammation to sustain the delivery (Mor et al. 2011). In terms of inflammatory mediators, the early implantation is characterised by a high level of proinflammatory T helper (Th)-1 and cytokines (IL-6, IL-8, TNFα) produced by both endometrial cells and immune cells recruited (65–70% uterine-specific natural killer (NK) cells, 10–20% are macrophages, and 2–4 % are dendritic cells). NK cells in human decidua regulate the trophoblast invasion by the secretion of IL-8 and interferon-inducible protein-10 chemokines (Mor et al. 2011).

The regulation of the cytokine networks is thus essential to prevent the rejection of the fetal allograft, and alterations in this pathway can result in adverse outcomes including miscarriage, preterm labor, preeclampsia, and intrauterine growth restriction (Challis et al. 2009).

1.4.2.1.3. Obesity during pregnancy

The Institute of Medicine (IOM) defines obesity during pregnancy as condition characterisd by a pre-pregnancy BMI ≥ 30 kg/m^2 and recommend gestational weight gains of 5-9 kg (Nascimento et al. 2011). During pregnancy, obesity is associated with an increased risk in adverse clinical outcomes and mortality for both mother and fetus. Adverse maternal outcomes include gestational diabete mellitus, gestational arterial hypertension and pre-eclampsia, venous thromboembolic disease, induction of labour and caesarean section, clinical and surgical complications (e.g., infections, haemorrhage, anaemia, urinary tract infection and endometritis), stress urinary incontinence, depression and even difficulties with breastfeeding. The mother obesity was also associated with adverse neonatal outcomes, such as macrosomia, metabolic syndrome and a predisposition to obesity secondary to gestational diabetes in children, in addition to neural tube defects and congenital anomalies (Nascimento et al. 2011).

1.5. Improving Quality of Life and Bio-molecular Profile

1.5.1. Physical Activity, the wonder cure

Physical activity (PA) is defined as "*any bodily movement produced by skeletal muscles that requires energy expenditure*" (World Health Organization 2020). It can be performed at various intensities, as part of work or domestic chores, leisure time (play, games, sports, or planned exercise), transportation (wheeling, walking, and cycling) and in the context of daily occupational, educational, home and community settings (World Health Organization 2020). Exercies can be instead defined as "*a subcategory of PA that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective. "Exercise" and "exercise training" frequently are used interchangeably and generally refer to physical activity performed during leisure time with the primary purpose of improving or maintaining physical fitness, physical performance, or health*" (World Health Organization 2020). PA is, thus, an integral part of human life and plays an essential role across the lifespan in the development and in the overall health regulation (Bamman et al. 2014; Neufer et al. 2015). On the opposite, sedentary behaviour is defined as "*any waking behaviour while in a sitting, reclining or lying posture with low energy expenditure*" (Tremblay et al. 2017).

In an evolutionary perspective, the ability to perform PA was essential to the human daily survival, leading to the implementation of adaptive biological responses to both acute and repeated PA episodes (Neufer et al. 2015). It is thus not surprising that the reduction or lack of PA can result in detrimental consequences on human health, whereas the regular exercise training has beneficial effects (Neufer et al. 2015).

However, radical changes have occurred over time concerning the evaluation of the relationship between PA and health. In ancient times, physicians such as those operating in the ancient China (XXVII century BC) and Hippocrates (V century BC) believed that PA had a great value for health (Lee et al. 2012). Specifically, Hippocrates was also the first in the Western culture highlighting the fundamental role of an active lifestyle, stating that "*if there is a deficiency in food and exercise, the body will fall sick*" (Murphy, Watt, and Febbraio 2020). By the twentieth century, instead, the common narrative was that exercise could be somehow dangerous, and the complete bed rest was a common prescription even for the treatment of non-communicable diseases (NCDs)

(Lee et al. 2012). The first rigorous, epidemiologic study investigating the relationship between PA and chronic disease risk was published in 1953, and since then a huge body of evidence have demonstrated the many benefits of PA on health (Lee et al. 2012). Nowadays, there are no more doubt that if PA were a drug, it would be a "*miracle cure*", with a dose-response relationship (**Figure 1**), better effects than many drugs in addressing common health issues and without the side effects of many pharmacological treatments (McNally 2020). PA can thus be considered as a natural therapy to cope also with imbalances tributable to common unhealthy lifestyles (Burini et al. 2020).

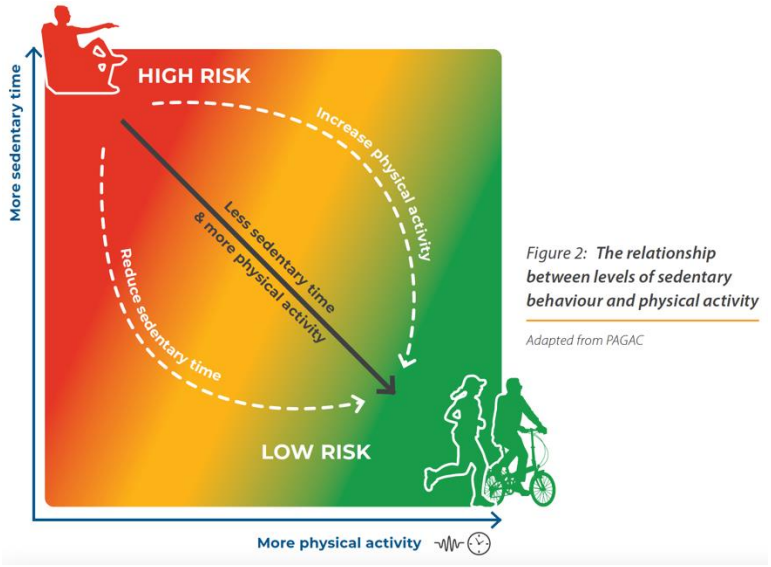


*Figure 2: **The relationship between levels of sedentary behaviour and physical activity***

Adapted from PAGAC

Figure 1: The dose-response curve of PA, highlighting absence of a lower threshold (in the left part of the curve) and that the highest benefits could be reached in more active people (in the right part of the curve - World Health Organization 2020)

Regular PA, indeed, is a known protective factor for cardiometabolic wellness, improves cognitive performance, and is effective in the prevention and management of a variety of health conditions, such as cardiovascular and neurological diseases, type-2 diabetes, breast and colon cancer, sarcopenia, osteoporosis, and mental health, and plays a key role in the healthy weight maintenance, muscle mass building, and preservation of musculoskeletal functions during aging, as long as in the improvement of general well-being (World Health Organization 2020; Christianson and Shen 2013; Neufer et al. 2015). More recently, the regular PA was found to be a protective factor able to reduce the illness severity and the mortality in COVID-19 patients (Sittichai et al. 2022).

The regular practise of exercise is thus fundamental in the general population, as well as in specific population groups, in which the definition of tailored programs is essential in promoting the adoption of helthy behaviours (Wada, Matsumoto, and Hagino 2019; Neufer et al. 2015) (**Figure 2**).

Outcomes (in alphabetical order)	Children and adolescents aged 5–17 years: PA and sedentary	Adults aged 18–64 years: PA	Adults aged over 18 years: sedentary	Adults aged over 65 years: PA[a]	Pregnancy and postpartum	Chronic conditions[b]	Children and adults with disability[c]
Adiposity (weight gain, weight change, weight control, weight stability, weight status and weight maintenance)	Critical	Critical	Critical	Critical[a]	Critical	Critical – HIV	–
Adverse events	Critical	Critical	–	Critical[a]	Critical (fetal outcomes)	–	–
All-cause and cause-specific mortality	–	Critical (cancer and CVD specific)	Critical	Critical[a]	–	Critical	–
Bone health	Critical	–	Important	–	–	–	–
Cardiometabolic health	Critical	–	–	–	–	–	–
Cognitive outcomes	Critical	Critical	Important	Critical[a]	–	–	Critical – MS, PD, Stk, Sch, ADHD
Delivery complications	–	–	–	–	Important	–	–
Disease progression	–	–	–	–	–	Critical – HT, T2D, HIV, Critical – cancer recurrence	–
Falls and fall-related injuries	–	–	–	Critical	–	–	–
Fetal outcomes (birthweight, preterm birth)	–	–	–	–	Critical	–	–
Functional ability	–	–	–	Critical	–	–	–
Gestational diabetes mellitus	–	–	–	–	Critical	–	–
Gestational hypertension/ preeclampsia	–	–	–	–	Critical	–	–
Health-related quality of life	–	Important	Important	Important[a]	–	Critical – HT, T2D, HIV	Critical – MS, SCI, ID, MCD, Sch
Incidence of cancer	–	Critical	Critical	Critical[a]	–	–	–
Incidence of CVD	–	Critical	Critical	Critical[a]	–	–	–
Incidence of hypertension	–	Important		Important[a]	–	–	–
Incidence of type-2 diabetes	–	Critical	Critical	Critical[a]	–	–	–
Mental health (symptoms of anxiety and depression)	Critical	Critical	Important	Critical[a]	Critical	–	–
Osteoporosis	–	–	–	Critical	–	–	–
Physical fitness	Critical	–	Important	–	–	–	–
Physical function	–	–	Important	–	–	Critical – HT, T2D, HIV	Critical – MS, SCI, ID, PD, Stk
Pro-social behaviour	Important	–	–	–	–	–	–
Psychosocial outcomes	–	–	–	Important	–	–	–
Risk of co-morbid conditions	–	–	–	–	–	Critical – HT, T2D, HIV	Critical – MS, SCI, ID
Sleep	Important	Important	Important	Important[a]	–	–	–

* Critical outcome: an outcome that is critical to decision-making; Important outcome: an outcome that is important, but not critical to decision-making.

[a] The critical and important outcomes considered for the adult population, including older adults.

[b] Outcomes are for subpopulation condition as listed: Cancer – cancer survivors; HT – hypertension; T2D – type-2 diabetes; HIV.

[c] Outcomes are for subpopulation condition as listed: MS – muscular sclerosis; SCI – spinal cord injury; ID – intellectual disability; PD – Parkinson's disease; Stk – in stroke survivors; Sch – schizophrenia; ADHD – attention deficit/hyperactivity disorder. Critical and important outcomes for the age-specific population were considered and extrapolated.

Figure 2: Benefits of a regular physical activity in various population subgroups (World Health Organization 2020).

According to the more recent esteems, every year between four and five million deaths could be averted if the global population was more active, with disparities in different areas around the world (Strain et al. 2020; Lee et al. 2012). According to the WHO, in 2016 the 27.5% of adults and the 81% of adolescents worldwide did not meet the recommendations, and only a limited global improvement could had been observed during the past decade (World Health Organization 2020). Women were reported to be less active than men in most of the countries, and significant differences PA levels were identified within and between countries and regions, likely due to inequities in the access to opportunities to be physically active (World Health Organization 2020). Moreover, the transition towards occupational and recreational activities ever more sedentary and the common use of motorized transportation increased the prevalence of sedentary behaviour

across the world (Litchfield et al. 2016; World Health Organization 2020). To promote the adoption of healthier lifestyle around the world and the value of regular PA in achieve this goal, the Global action plan on PA 2018–2030 sets out 4 strategic objectives and 20 policy actions to achieve a 15% relative reduction in the global prevalence of physical inactivity in adults and adolescents by 2030 (World Health Organization 2020).

1.5.1.1. Physical Activity and Health

Physical inactivity might be considered the biggest public health problem of the current century (Burini et al. 2020). The harmful role of physical inactivity is now well established, with a large body of evidence demonstrating its role in enhancing obesity, accumulation of visceral fat, insulin resistance, hyperlipidaemia and skeletal muscle atrophy, and its role as risk factor for colon, endometrial and breast cancers, type 2 diabetes, cardiovascular disease, bone degenerative diseases, diseases involving cognitive impairment (such as dementia), and polycystic ovarian syndrome (Pedersen and Febbraio 2012; Murphy, Watt, and Febbraio 2020).

In adults, regular PA is associated with an improvement in several health outcomes, such as all-cause mortality, cardiovascular disease mortality, incident hypertension, site-specific cancers, and type-2 diabetes, mental and cognitive health, sleep, and adiposity (World Health Organization 2020). Being physically active, indeed, reduces a person's risk of dementia by 30%, depression by 30%, heart disease by 40%, type 2 diabetes by 40%, breast cancer by 25% and osteoporosis by 50% (McNally 2020).

These impressive results are due to the key role of PA in promoting several physiological responses leading to beneficial short- and long-term autonomic and haemodynamic adaptations. (World Health Organization 2020). More specifically, evidence reaffirmed the key role of PA in reducing blood pressure in both adults with prehypertension and normal blood pressure, and in reducing by even the 10–20% the incidence of type-2 diabetes, with a decreasing slope at higher levels of physical activity (King et al. 2019).

Engaging in regular PA have beneficial effects also for mental health, reducing the risk of developing anxiety and depression, improving cognition (*e.g.*, processing speed, memory, and executive function), brain function and structure, and reducing the risk of developing cognitive impairment, including Alzheimer's disease (Schuch et al. 2019; 2018; King et al. 2019). Specifically concerning this last relationship, the beneficial effects were achieved performing different types of PA including aerobic activity, walking, muscle-strengthening activity, and yoga (Northey et al. 2018).

PA bouts, both acute and regular, were reported to have a positive effect also in improving sleep and health-related QoL outcomes (King et al. 2019).

Moreover, the regular practise of exercise is essential in the treatment of most common conditions, being associated with a reduction of complications and an improvement in QoL (McNally 2020).

1.5.1.2. WHO Guidelines

The recommendation for adults (18-64 yrs.) by the WHO included in the last *WHO guidelines on physical activity and sedentary behaviour* (2020), are (World Health Organization 2020):

- *All adults should undertake regular physical activity.*
- *Adults should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits.*

- *Adults should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.*
- *Adults may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits*.
- *Adults should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.*
- *To help reduce the detrimental effects of high levels of sedentary behaviour on health, adults should aim to do more than the recommended levels of moderate- to vigorous intensity physical activity.*

1.5.1.3. Physical Activity in improving the Quality of Life

The regular practice of PA was reported to be effective in increasing self-efficacy, which may "spill over" to other life domains. Concerning the working environment, active employees may consequently feel more competent with their tasks, and perceive them as less demanding (Naczenski et al. 2017). Exercise, indeed, may have a role in modulating neurotransmitters and neuromodulators, increasing the ability to deal with psychological stress and recovery after the exposure, and resulting thus in better mood and increased energy (Naczenski et al. 2017). Furthermore, PA may be helpful in building cognitive resources, such as executive functions and memory, and in restoring those lost during the workday, enhancing the resistency and resiliency to high job demands and aiding recovery (de Vries and Bakker 2022). As consequence, the regular practice of exercise training may lead to the lasting of positive affective states in preference to the negative ones, such as stress and depression (Basso and Suzuki 2017; DIshman, McDowell, and Herring 2021). PA may also play a fundamental role in building social resources, such as in the creation of stronger social networks, which are well-established to be related with the ability to cope with stressful situations (de Vries and Bakker 2022). Finally, PA may also improve mastery experiences and personal control over the environment, resulting in an increased self-efficacy (de Vries and Bakker 2022)

1.5.1.4. Physical Activity in improving Bio-molecular Profile

The exact molecular pathway by which PA actively play its role in health promotion still remain poorly understood. Indeed, PA was estimated to be ∼40% more protective than what could be predicted by the analysis of the direct modulation induced in the traditional risk factors, such as blood lipids, hypertension, diabetes etc. (Joyner and Green 2009).

Several mechanisms have been identified, including weight loss, increased cardiorespiratory fitness, the maintenance of muscle mass, and the engagement of the sympathetic neural circuitry and the neuroendocrine systems to coordinate adjustments in respiration, blood flow, fuel supply, and thermoregulation (Pedersen and Febbraio 2012; Neufer et al. 2015). At molecular level, PA enhance the interorgan communication based on a broad range of exercise-related humoral factors involving, besides those produced in muscles, molecular messengers from heart, liver, white and brown adipose tissues, and nervous system, with autocrine, paracrine, and endocrine effects (Chow et al. 2022). The vast majority of the long-term positive effects of PA are thought to arise from adaptive changes in the activity and/or abundance of proteins involved in specific metabolic, physiological, and biomechanical processes (Neufer et al. 2015).

In energetic terms, it is fundamental to have a match between the activity demands and the suitability of the response, since an insufficient demand can limit the ability to achieve goals, while when excessive, it can limit the efficiency and the sustainability of the response (Neufer et al. 2015). The physiological network can thus rely on huge reserve capacity and have a remarkable flexibility allowing it to operate in a dynamic continuum (Neufer et al. 2015).

Among this huge variety of pathways involved, a key role in the relationship between PA and health is played by the nervous and immune systems, even though the link between the the functionality enhancement and the resistence to diseases has yet to be clarified. Indeed, the neuronal networks is involved in the control of the dynamic of the PA response (i.e., the initiation, intensity, duration, and termination of PA) and in the response of the different organs (Neufer et al. 2015).

The relationship between the PA and the inflammatory status has instead many facets. The immune system polarizes the response to PA by modulating myokine levels, *i.e.* cytokines synthesized and released by muscle tissue in response to muscle contraction (Goudreau et al. 2021). Indeed, PA inactivity and abdominal adiposity are associated with a chronic low-grade inflammation at systemic level, which is independent of the eventual obesity status (Burini et al. 2020). A growing literature has thus far demonstrated an anti-inflammatory effect from regular PA and exercise, even thoug PA itself act as a stressor able to eliciting the expression of pro-inflammatory cytokines (Burini et al. 2020; Cerqueira et al. 2020).

Exercise is, indeed, able to initiate a cascade involving inflammatory mediators, and these changes can be divided into acute effects, occurring immediately after an exercise bout and depending on the type, intensity, duration and familiarity of the exercise, and on the age and clinical status of the subject, and long-term effects, affecting the basal resting level (Cerqueira et al. 2020). PA induce a tipycal anti-inflammatory profile (Pedersen and Febbraio 2012). Specifically, PA lead at first to the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and then of anti-inflammatory ones (IL-4, IL-10, IL-1RA, and IL-13) attenuating the response (Moldoveanu, Shephard, and Shek 2001).

Specifically, the release of IL-6 is highly sensitive to PA. The persistence of high IL-6 levels was reported to be related to muscle atrophy and impairment in muscular functions (Hennigar, McClung, and Pasiakos 2017). PA itself leads to an increase in IL-6 levels, both due to muscular damage and independently to this condition (Lightfoot and Cooper 2016; Burini et al. 2020).

Intense exercise can lead also to an increase in IL-10 (Allen, Sun, and Woods 2015), even if the evidences reported in literature are controversial (Shaw et al. 2018). The concentration of this cytokine reaches the peak during recovery time, and it depends on the exercise intensity. However, the rise in IL-10 levels could be associated to the prevention of detrimental damages to the tissues and chronic low-grade inflammation (Cerqueira et al. 2020).

PA was shown to be able to lead also an increase in the release in IL-8 even after moderate and high-inensity exercise (Cerqueira et al. 2020).

The role of PA on the immune system these days assumes a pivotal role, being PA one of the behavioural factors associated with an enhanced vaccine response (Pascoe, Fiatarone Singh, and Edwards 2014). Active people are indeed more likely to experience a better immune response, with higher efficacy in regularly trained subjects who had an exercise session shortly before inoculation (Bortolini et al. 2022). The recent COVID-19 pandemic shed light on the importance of immunisation campaigns, and the PA is proving once more to be essential in the promotion of health and well-being.

1.5.1.5. Physical Activity Promotion Strategies

The ultimate achievement of prevention programs based on the promotion of a regular exercise training is to maximize the long-term beneficial effects for the subjects involved (*e.g.*, reestablishing energy balance, improving cardiorespiratory capacity, increasing muscle and/or bone mass/strength, improving cholesterol/lipoprotein profiles, etc.) (Neufer et al. 2015).

Aiming to offer an intervention as inclusive as possible, there must be a specific focus on several baseline characteristics which may variously influence the participation, the effectiveness of the intervention and, in the end, the health benefit, such as the initial level of fitness, age, sex, genetic/epigenetic factors, nutritional state, health condition (cancer, diabetes, cardiovascular disease, COPD, etc.), eventual pregnancy, and prescription drugs (Neufer et al. 2015).

Several studies to date have highlighted that pregnant women are more prone than non-pregnant to adopt a sedentary behaviour (Löf 2011). This choice was found to be related not only to the need to cope with pregnancy-related symptoms (*e.g.* lumbopelvic pain, psychological issues, and gestational weight gain), but also to the lack of time and to a misconception about the eventual detrimental effect of exercise training on fetal health, such as an increase in the risk of miscarriage (Evenson and Bradley 2010; Chan, Yeung, and Law 2019). These beliefs are embedded in the culture systems, and can be different among women from different countries (Guelfi et al. 2015).

Quite the opposite: PA in pregnant women have a number of benefits, often underestimated. Exercise training was reported, indeed, to be related to the maintenance of the vascular function of the placenta, a reduced risk of depression, an improvent in cardiorespiratory fitness, QoL, body image satisfaction and self-esteem (K. Chen et al. 2022).

However, the adoption of a healthy diet is perceived as more effective than the engagement in exercise training, and relaxation is perceived as a safer behaviour (Guelfi et al. 2015).

A further element which can play a role in dishearten the engagement in PA could be that only a small percentage of physicians helps their patients to prepare PA programs, providing the required information for building an effective and safe tailored plan in terms of types of exercise and load, and excluding medical conroindications (Krzepota, Sadowska, and Biernat 2018).

2. Systematic Review

2.1 Material and methods

2.1.1. The Protocol

The systematic review was implemented in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) 2020 statements (Page et al. 2021). The protocol was developed *a priori* and registered on the *International prospective register of systematic reviews* (PROSPERO) to make it publicly available on the 24th October 2020 (Protocol n. CRD42020210876 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020210876). Due to the increase in submissions during the pandemic and the necessity for the PROPSPERO working group' to prioritise registrations related to COVID-19, the eligibility of the protocol was checked by the PROSPERO auto-processing system. However, as stated by the PROSPERO team, the records deemed eligible and published on the website should not be treated differently as a result of being automatically published.

The systematic review was intended to provide the state of art of the simultaneous assessment of the QoL and bio-molecular profile in workers, highlighting, whether possible, the link among these domains, apparently very distant from each other.

The aim was to answer the following research question: "*How work is able to influence workers' Quality of Life and bio-molecular profile?*", and more specifically:

- *Are Working Conditions able to influence the workers' Quality of Life perception and bio-molecular profile?*
- *Are the alterations in Quality of Life perception and in bio-molecular profile ascribable to the quality of working conditions?*

The research question was built following the PICO model, as detailed in **Table 1:**

Patient/Population	**I**ntervention(s)/Exposure(s)	**C**omparator(s)/control	**O**utcomes
Adult workers (regardless age groups, sex, professions, and qualifications)	All kinds of working conditions, job characteristics, or work-related factors	Presence/absence of occupational stress, job demands vs resources, mental vs physical work, precarious vs stable employment, shift work vs non-shift work, work-family conflict vs absence of conflict.	• Quality of Life assessment measured by internationally validated tests; • Bio-molecular profile assessment (oxidative stress biomarkers, inflammatory biomarkers, cortisol, melatonin) in various biological matrices.

Table 1: The PICO model

The comparators listed in the *a priori* protocol were not employed in the data analysis due to the absence of proper data in the selected articles.

2.1.2. Study Selection

The query of the original search articles was launched on the 11th May 2020 in PubMed, on three electronic databases: PubMed, Embase, Cochrane CENTRAL. The 3rd March 2022 the search was repeated to include possibly eligible articles published in the meantime.

The search strings was created in collaboration with the *Federated Library of Medicine "F. Rossi", (University of Turin)* and include the following terms: "Oxidative Stress", "Hydrocortisone", "Malondialdehyde", "8-Hydroxy-2'-Deoxyguanosine", "F2-Isoprostanes", "C-Reactive Protein", "Interleukin-6", "Interleukin-8", "Interleukin-1", "Tumor Necrosis Factor-alpha", "Melatonin", "Quality of Life", "Work", "Employment", "Occupations", "Job Satisfaction", "Occupational Stress", "Occupational Exposure", "Occupational Health", "Occupational Groups".

The full strings are provided in the **Appendix A**.

2.1.3. Inclusion and Exclusion Criteria

All those articles, in English or Italian, engaging adult workers (18+ years) and including both QoL and bio-molecular profile assessment published until the 3rd March 2022 were considered potentially eligible, regardless their age, sex, occupation and qualification.

The exclusion criteria were: (i) epidemiological samples including unemployed subjects or workers under 18 years old not analysed separately; (ii) non-research articles (reviews, editorials, commentaries, protocols, conference abstract, etc.).

The screening was performed in a blind process by two reviewers, according to the eligibility criteria above detailed, and eventual disagreements were subjected to the judgement of a third reviewer.

2.1.4. Data Extraction

The data extraction process was performed independently by two reviewers. Data extracted included: articles details (authors, year of publication, title, journal, country), study characteristics (setting, design, composition, and sample size), epidemiological sample characteristics (age, sex, eventual disorders or pathologies, ethnicity, lifestyle), QoL assessment (type of questionnaire and outcome scores), working activity characteristics (working activity, working years, working condition assessment), bio-molecular profile assessment (the type of biomarker, analytical method, biological specimen, and outcome), co-factors/confounding factors, adjusted relative risk or odds ratio, suggested mechanisms of action, suggested interventions, limitations, and conclusions, eventual conflict of interest.

Eventual missing data were requested to the corresponding authors of the published articles. Data displayed only by graphs were extracted by the WebPlotDigitizer software (https://apps.automeris.io/wpd/) (accessed on 17 May 2022).

2.1.5. Quality Assessment

The risk of bias was performed in a blind process by two reviewers, employing the appropriate Critical Appraisal Checklist according to the study design of the eligible articles. Specifically, Joanna Briggs Institute (JBI) checklists was employed for cross-sectional and randomised controlled trials, while the NIH Quality assessment Tool was employed for the before after studies. The JBI checklist for case series was employed for a study based on an N-to-1 design, considering only appropriate questions.

The response to checklists were transformed in a Completeness of Reporting Score (COR), according to the number of items satisfied. COR was calculated as:

$$COR\ (\%) = \frac{items\ satisfied}{items\ not\ or\ unclearly\ satisfied} \times 100$$

Each study was then awarded by a quality judgment according to the COR score: “poor” (if <50% of items were met), “moderate” (if 50–74% of items were met), or “high” (if ≥75% of items were met) (B. Suvarna et al. 2020). Only studies with a “moderate” or “high” quality were included in the review.

2.1.6. Statistical Analysis

Categorical variables have been reported as frequency (*n*), while continuous variables have been reported as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM) or median and interquartile range (IQR). Graphs were created by R Studio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA).

2.2. Results

2.2.1. Search Results

The search in the three databases provided 10,375 items totally. The **Figure 3** summarises the study selection process and the number of articles analysed in each step. In the end, 23 articles fulfilled the inclusion criteria and were included in the present systematic review (Devoto et al. 2017; Gill et al. 2014; Heinzelmann et al. 2014; Kanefsky et al. 2019; Knuth et al. 2016; Nieuwenhuijsen et al. 2017; Sandström et al. 2011; Schaffer et al. 2019; Ebata, Tatsuta, and Tatemichi 2017; Everding et al. 2016; Feicht et al. 2013; Giessing et al. 2020; Harris et al. 2007; Jordakieva et al. 2022; Kasemy et al. 2020; Nickel et al. 2007; Ozyurek et al. 2021; Sudheeran et al. 2016; Poon et al. 2018; Rector et al. 2014; Rosemberg et al. 2019; Sadowska et al. 2021; Vlahoyiannis et al. 2022). The 52.2% (*n*=12) of them were awarded with a "high" quality score, while the 47.8% (*n*=11) were judicated to have a "moderate" quality.

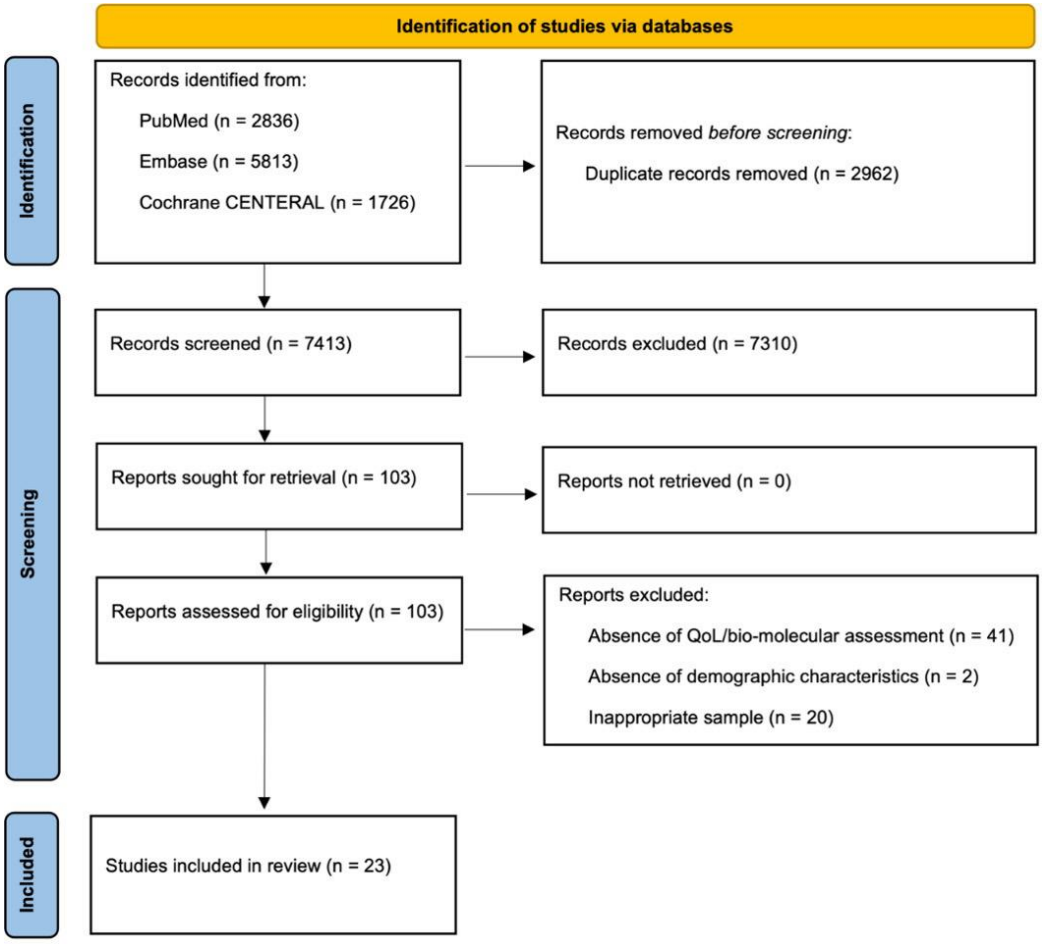


Figure 3: PRISMA flow diagram summarising the literature query and the study selection process.

2.2.2. Epidemiological Sample

In the 23 studies included we observed a high diversity in terms of subjects' characteristics and occupation types. Since some studies included subjects fulfilling the inclusion criteria but showing symptoms of overt mental distress, we decided to split the epidemiological sample into a "*clinical*" and a "*non-clinical*" group, to preserve the original value of data. By "*clinical population*" we meant those subjects having received a diagnosis for psychological disorders that could be related to

working activities. A brief synopsis of the included studies (country, population characteristics, QoL questionnaire administrated, biological matrix and biomarkers analysed, and the quality assessment score assigned) in each group is reported in **Tables 2** and **3**.

Authors, Year	Country	Sample Population and Diagnosis	QOL Questionnaire	Biological Matrix and Biomarkers	Quality Assessment
Devoto et al., 2017	US	Active duty military personnel; Traumatic Brain Injury	SF-36 ↓ emotional wb, energy/fatigue, health perception, em. role limit, ph. role limit, social functioning; ≈ bodily pain, ph. functioning	Blood ↑TNF-α, IL-6; ≈ IL-10	High
Gill et al., 2014	US	Active duty military personnel; PTSD, Depression, Traumatic Brain Injury	SF-36 ↓ total, all domains	Blood ↑ IL-6, CRP	High
Heinzelmann et al., 2014	US	Military personnel; Insomnia, Depression, PTSD	RAND-36 ↑ ph. functioning, social functioning, emotional wb, energy/fatigue	Blood ↓ CRP; ≈ IL-6	Moderate
Kanefsky et al., 2019	US	Active duty military personnel; Traumatic Brain Injury	SF-36 ↓ all domains	Blood ↑ IL-6; ≈ IL-10, TNF-α	Moderate
Knuth et al., 2016	BR	Community Health Agents; Depression	WHOQOL-Bref ↓ physical, environmental domains	Saliva ↑ Cortisol	Moderate
Nieuwenhuijsen et al., 2017	NL	Professionally active adults; Neurasthenia	SF-36 ≈ all domains	Hair ≈ Cortisol	Moderate
Sandstrom et al., 2011	SE	Workers with work-related exhaustion; Burnout	WHOQOL-Bref ↓ psychological, environmental domains	Urine ≈ Cortisol Saliva ≈ Cortisol Blood ↑ IL-1β; ≈ TNF-α, IL-1Ra, IL-6	High
Schaffler et al., 2013	D	Professionally active adults; Asthenia/Fatigue	WHO-5 ≈	Saliva ↓ Cortisol	Moderate

Table 2. Summary of characteristics of the articles ascribed to the "*Clinical population group*".
TNF-α = Tumor Necrosis Factor alpha; IL = Interleukin; CRP = C-reactive protein; IL-1Ra = Interleukin 1 Receptor Antagonist.

Authors, Year	Country	Sample Population	QOL Questionnaire	Biological Matrix and Biomarkers	Quality Assessment
Devoto et al., 2017	US	Active-duty personnel	SF-36	Blood TNF-α; IL-6, IL-10	High
Ebata et al., 2017	J	Public employees, Nurses, Office workers	SF-8 ≈	Blood ↑ BAP ≈ d-ROM	Moderate
Everding et al., 2016	US	Sworn officers	Unhealthy Days ↓	Blood ≈ IL-6, IL-10, TNF-α, IL-1β, IL-4, IL-8, TGF-α, TNF-β	High
Feicht et al., 2013	D	Insurance company employees	WHO-5 ↑	Saliva ≈ Cortisol ↓ α-amylase	Moderate
Giessing et al., 2020	DE	Patrol police officer	SF-36; WHO-5	Saliva Cortisol; α-amylase	High
Harris et al., 2007	NO	Nursing staff	SF-36	Saliva Cortisol	High
Jordakieva et al., 2021	AT	Hospital workers	WHOQOL-Bref ≈	Blood ≈ CRP, IL-6	High
Kanefsky et al., 2019	US	Active duty military personnel	SF-36	Blood IL-6; IL-10; TNF-α	Moderate
Kasemy et al., 2020	EG	Physicians; Nurses; Non-Health Care Workers	WHOQOL-Bref ↓	Blood IL-6, TNF-α	High
Nickel et al., 2007	A	Blue collar; white-collar; self-employed	SF-36 ↑	Saliva ↓ Cortisol	Moderate
Özyürek et al., 2020	TR	Nurses	SF-36; SWLS	Blood—TOS; TAS; Cortisol	High
Pandaran Sudheeran et al., 2016	IND	Private company employees	SF-36 ↑ overall mean	Blood ↑ CAT, SOD, GPx, Glutathione; ↓ MDA	High
Poon et al., 2018	HK	Jockeys	WHOQOL-Bref ≈	Blood ≈ Cortisol	Moderate
Rector et al., 2014	D	Employees	SF-12	Blood CRP Saliva Cortisol	Moderate
Rosemberg et al., 2019	US	Hotel housekeepers	SF-12 ↓	Blood Allostatic Load Index; CRP; Cortisol	High
Sadowska et al., 2020	PL	Professional caregivers	WHOQOL-Bref ≈	Blood ≈ IL-6, CRP; ≈ Cortisol	Moderate
Vlahoyiannis et al., 2022	GR	Nurses	SF-36 ↓	Saliva ≈ Melatonin	High

Table 3. Summary of characteristics of the articles ascribed to the "*Non-clinical population group*". *TNF-α = Tumor Necrosis Factor alpha; IL = Interleukin; CRP = C-reactive protein; IL-1Ra = Interleukin 1 Receptor Antagonist*; *BAP = Biological Antioxidant Potential; CAT = Catalase; dROM = diacrons reactive oxygen metabolic; GPx = Glutathione Peroxidases; GSH = Reduced Glutathione; MDA = Malondialdehyde; SOD = Superoxide Reductase; TOS = Total Oxidant Status; TAS = Total Antioxidant Status; NA = Neuroendocrine Activation*.

2.2.3. Biomarker Selection

In the articles included a total number of 22 biomarkers were assessed. The biological matrices employed were blood, saliva, hair, and urine, and the biomarkers analysed were a proxy of three molecular pathways (*i.e.,* oxidative stress, inflammation, and neuroendocrine activation), as reported in **Figure 4**.

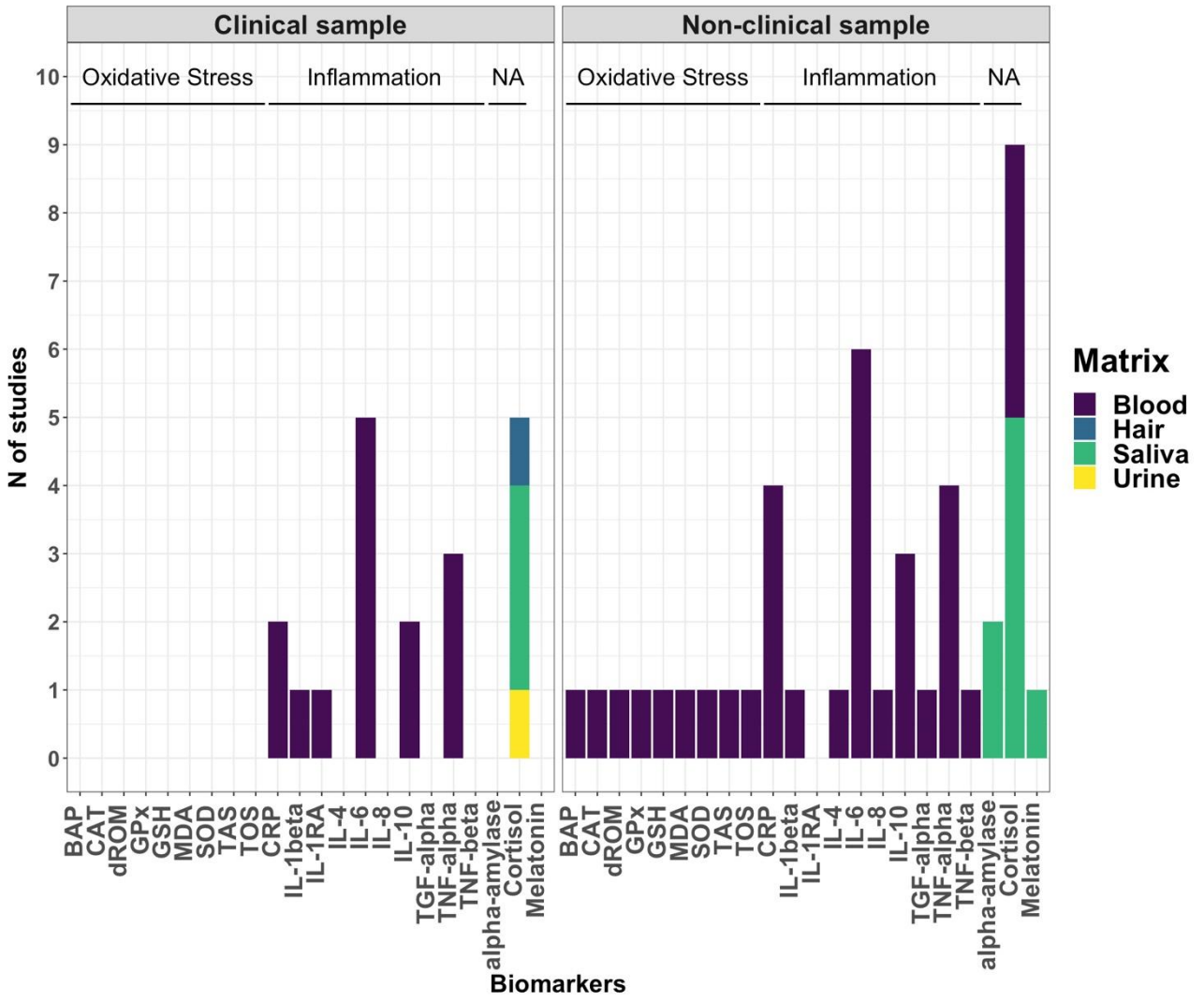


Figure 4: Biomarkers assessed and their frequency in the studies included in the review. *BAP = Biological Antioxidant Potential; CAT = Catalase; dROM = diacrons reactive oxygen metabolic; GPx = Glutathione Peroxidases; GSH = Reduced Glutathione; MDA = Malondialdehyde; SOD = Superoxide Reductase; TOS = Total Oxidant Status; TAS = Total Antioxidant Status; CRP = C-Reactive Protein; IL- = Interleukin; NA = Neuroendocrine Activation.*

2.2.4. Quality of Life Assessment Method Selection

The QoL of the subjects enrolled were assessed by seven different questionnaires, as can be seen in **Figure 5**.

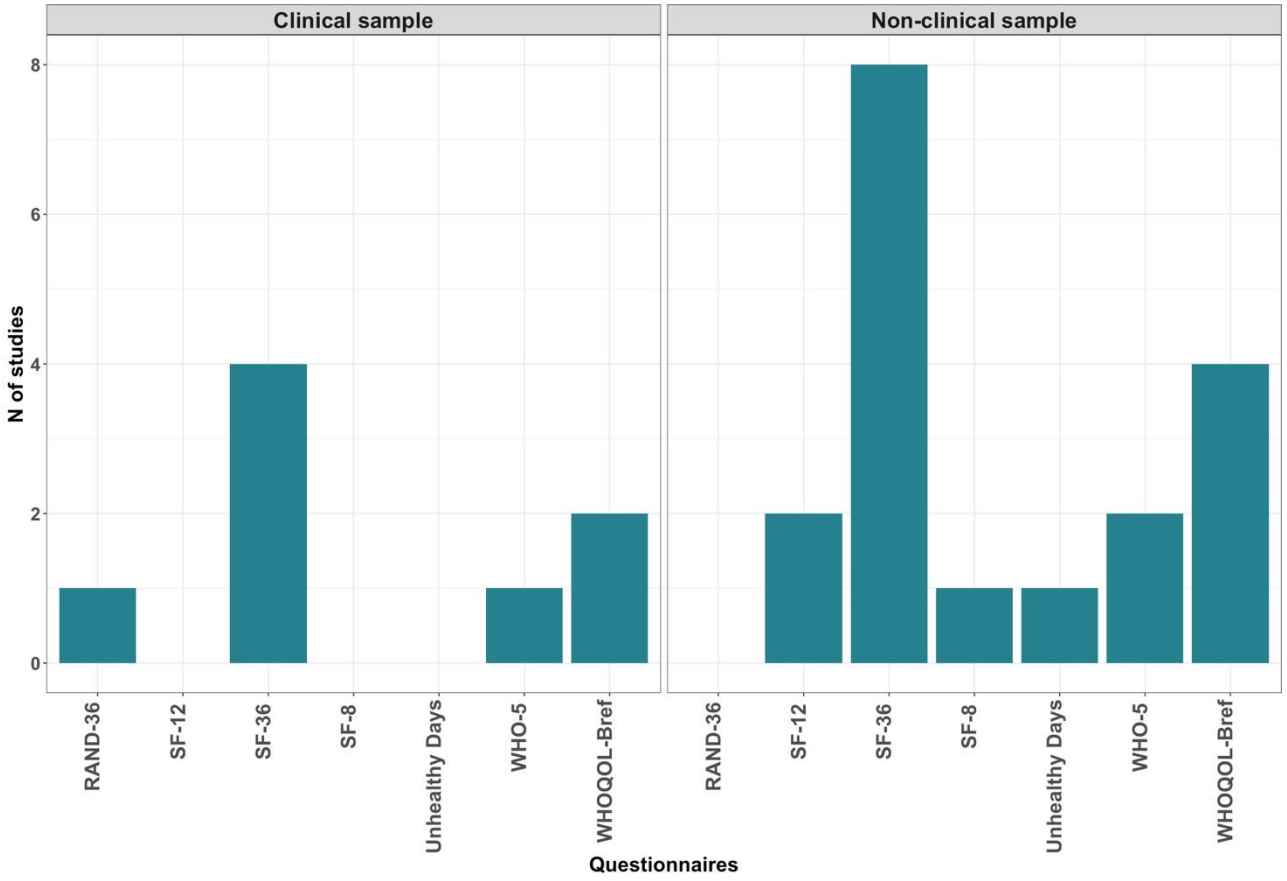


Figure 5: Questionnaires employed and their frequency in the studies included in the review.

2.2.5. Clinical Population

2.2.5.1. Inflammatory Biomarkers

In a study on TBI aftermath in military personnel, Devoto et al. found higher blood levels of IL-6 and TNF-α in the TBI group than in controls ($p = 0.007$ and $p = 0.003$, respectively), while no difference was reported in IL-10 levels. Comparing the SF-36 questionnaire domain scores, the TBI group reported lower levels for emotional well-being ($p = 0.001$), energy/fatigue ($p = 0.007$), health perceptions ($p = 0.001$), emotional role limitations ($p = 0.035$), physical role limitations ($p = 0.018$), and social functioning ($p = 0.003$). No differences were instead found for bodily pain (p = ns) and physical functioning (p = ns). The exploratory factor analysis performed in the TBI group to describe the latent relationship between emotional and physical health variables and the inflammatory profile revealed the high association between high inflammation (TNF- α, IL-6, IL-6/IL-10 ratio) and poor mental health (PTSD and depression). A high association was also found between low PTSD, depression, TNF-α, and QoL scores (SF-36 domains—bodily pain, high emotional functioning, emotional wellbeing, emotional role functioning, social functioning, vitality, and physical role functioning) (Devoto et al., 2017).

Gill et al., in a population of active-duty military personnel recently returned from operations in Iraq and Afghanistan, reported significantly higher values of IL-6 and CRP levels in the high comorbid group (2–3 service-related disorders among PTSD, depression, and TBI) than in the low comorbid group (0–1 service-related disorders) ($p < 0.01$ and $p < 0.05$, respectively). The relationship remains significant only for IL-6 after correction for sleep disorders ($p < 0.05$). The QoL assessment revealed lower scores in both the total SF-36 and in all the domain scores ($p < 0.01$). The further comparison between the groups with service-related disorders (TBI alone, PTSD and depression, and PTSD, depression, and TBI) and the no co-occurring group revealed an analogue difference ($p < 0.01$), except for the TBI alone group (p = ns). The IL-6 concentration was found to be significantly related to HRQOL, even after controlling for age, medications, and BMI. This relationship was found to be mediated by depression (22.3%, $p < 0.01$) and PTSD (19.1%, $p < 0.05$). On the contrary, no significant relationship was found between CRP and HRQOL (Gill et al. 2014).

Similarly, comparing military personnel with a history of TBI who experienced or did not have a concurrent Loss of Consciousness (LOC) and a control group, Kanefsky et al. reported a significant difference ($p < 0.001$) in plasma IL-6 levels, even after controlling for Combat Experiences Scale and insomnia status, with the highest levels found in the LOC group ($p < 0.001$). Specifically, insomnia was associated with a 0.37 pg/mL increase in IL-6 levels. No differences had been found instead for IL-10 and TNF-α levels. The QoL (SF-36) was lower in the TBI groups in all eight domains ($p < 0.05$). No association has been found between cytokine levels and self-reported QoL (Kanefsky et al. 2019).

In a similar population with all volunteers affected by insomnia, Heinzelmann et al. found a significant reduction in CRP plasma levels in those subjects following a standard-of-care intervention therapy (cognitive behavioural therapy, pharmacological agents, and/or auto-adjusting positive airway pressure treatment) ($p < 0.01$), while no effect was detected in IL-6 levels. As well, they reported an increase and a significant interaction effect between sleep groups and time in the subjects' QoL perception (RAND-36), specifically in the physical functioning ($p = 0.04$), the social functioning ($p = 0.03$), emotional well-being ($p = 0.03$), and energy/fatigue ($p < 0.001$) domains. For the last two domains, there was also a significant effect for time ($p = 0.05$ and $p = 0.03$, respectively) (Heinzelmann et al. 2014).

In a study on workers previously diagnosed with work-related exhaustion, Sandstrom et al. (2011) found significantly higher values of IL-1 ($p = 0.015$) than in a control group. As well, they reported lower levels in the Environment and Psychological domains of the WHOQOL-bref questionnaire ($p = 0.036$ and $p < 0.001$, respectively) (Sandström et al. 2011).

2.2.5.2. Stress Biomarkers – Hypothalamic-Pituitary-Adrenocortical Activity (Cortisol)

Knuth et al. (2016) reported higher cortisol levels in community health agents with less than 1 year of service compared to their colleagues with a longer career ($p = 0.026$) and a significant negative association between salivary cortisol levels and the WHOQOL-bref environmental domain score ($r = -0.214$; $p = 0.017$). No association was found with the other domains (physical, psychological, and social). The physical domain of QoL was significantly lower in those suffering accidents at work ($p = 0.007$) and in those perceiving health changes due to work ($p = 0.001$). Those having suffered accidents at work also reported lower scores in the environmental domain ($p = 0.008$) (Knuth et al. 2016).

In comparing women with stress-related exhaustion with healthy controls, Sandstrom et al. did not report significant differences in urinary and diurnal salivary cortisol concentrations (Sandström et al. 2011).

A trial involving workers affected by work-related stress by Nieuwenhuijsen et al. revealed that light plus electromagnetic therapy combined with coaching is not sufficient to induce a significant improvement in QoL (SF-36) and hair cortisol levels (Nieuwenhuijsen et al. 2017).

In a similar population, Schaffler et al. evaluated the potential role of Eleutherococcus senticosus (ES) administration in workers affected by stress-related fatigue, impaired work, or concentration, revealing a general trend supporting a possible superiority of treatments involving the combination of ES with classical Stress Management Therapy (SMT) in improving QoL (WHO-5, $p = 0.051$). The cortisol awakening response (i.e., the increase within 30 min after awakening) significantly changed during the time without group differences ($p = 0.047$) (Schaffer et al. 2019).

2.2.6. Non-Clinical Population

2.2.6.1. Oxidative Stress Biomarkers

In a study aiming to find potential objective biomarkers of fatigue in working women, Ebata et al. analysed serum concentrations of diacrons reactive oxygen metabolic (d-ROMs) and biological antioxidant potential (BAP). The authors highlighted significantly higher BAP levels in shift-workers compared with daytime workers. The relationship remained significant even after adjusting for age, BMI, commuting time, sleep, drinking/smoking, and VDT ($p < 0.001$). In shift-workers, the BAP level was even associated with the Visual Analysis Scale for "sensation of fatigue". No significant differences were reported in QoL (SF-8), on both mental and physical scales (Ebata, Tatsuta, and Tatemichi 2017).

Pandaran Sudheeran et al. developed a trial to evaluate the potential role of curcumin-based products in handling occupational stress among workers in responsible positions. After a 31-day supplementation with curcumagalactomannoside (CGM), the authors reported a significant increase in plasmatic levels of glutathione and antioxidants enzymes such as catalase, superoxide dismutase, and glutathione peroxidase ($p < 0.01$) and a decrease in MDA ($p < 0.001$). The supplementation with standard curcumin was reported to have a similar effect, but with lower efficacy ($p < 0.05$). As expected, no difference in these biomarker levels was found in the placebo group ($p = ns$). In the two intervention groups, a significant increase in QoL (SF-36) (CGM $p < 0.01$ and standard curcumin $p < 0.05$, respectively) can be observed, with the higher levels reached in the CGM group. As for the biomolecular profile, no significant variation in QoL perception was found in the placebo group (Sudheeran et al. 2016).

2.2.6.2. Inflammatory Biomarkers

In a study on law enforcement officers, Everding et al. grouped participants according to their sleep quality. No significant differences among the three analysed sleep quality groups (good, borderline, poor) were found in cytokine levels (IL-1, IL-4, IL-6, IL-8, IL-10, TGF-α, TNF-α, and TNF-α). In contrast, the QoL (unhealthy days) was reported to be significantly different among the three sleep groups ($p < 0.001$), with the subject reporting poor sleep experiencing a higher number of unhealthy days when compared with the other two groups ($p < 0.05$). As well, the poor sleepers were reported to have a higher OR for worsened mental health and impaired HRQOL ($p < 0.001$) (Everding et al. 2016).

Rector et al. attempted to evaluate the association between psychological stress and CMV antibody levels in an occupational sample. Systemic inflammation measured by CRP was not reported to be associated with infection status or CMV-Ig levels. In contrast, the authors found an association between lower QoL (SF-12) scores and increased CMV-Ig levels in CMV+ subjects ($p < 0.05$), even though any association was found with CMV infection (Rector et al. 2014).

Sadowska et al. did not find any difference in blood concentration of systemic inflammatory biomarkers in professional caregivers compared to healthy controls. As well, no significant difference was found in QoL scores (WHOQOL-Bref) (Sadowska et al. 2021).

Jordakeva et al., in an attempt to evaluate the role of shiftwork in health care professionals, did not find any difference in both QoL scores (WHOQOL-Bref) and inflammatory biomarkers (IL-6 and CRP) comparing day workers vs rotating night shift workers (Jordakieva et al. 2022).

The results of Kasemy et al., comparing health care workers vs white collars employed in the same facilities, revealed, instead, that health care professionals reported a significantly lower QoL scores (WHOQOL-Bref, $p < 0.001$), while the results of the comparison of the two groups according to the inflammatory biomarker concentration (IL-6 and TNF-α) were not reported (Kasemy et al. 2020).

2.2.6.3. Stress Biomarkers – Hypothalamic-Pituitary-Adrenocortical Activity (Cortisol)

In a study aiming to evaluate the role of a 7-week web-based happiness training in improving workers' psychological well-being, Feicht et al. did not find a significant variation in salivary cortisol due to the intervention. The comparison of QoL scores (WHO-5) revealed a significant increase in the intervention group after the training ($p < 0.001$), which resulted in significantly higher levels when compared to the control group ($p < 0.001$) (Feicht et al. 2013).

On the other hand, in a study on nursing staff, Harris et al. reported a positive correlation between daily cortisol in saliva and QoL (SF-36) domains. Specifically, they reported a positive correlation between cortisol decline and physical functioning, general health, and vitality ($p < 0.05$). This last was also negatively correlated with cortisol level at 10:00 p.m. ($p < 0.05$). Some working conditions were found to be correlated with cortisol. A positive association was found between awakening levels and both the decision latitude and decision authority, which was revealed to also be positively associated with cortisol decline during the day (both $p < 0.05$) and negatively correlated with awakening cortisol response ($p < 0.05$) and evening cortisol levels ($p < 0.01$). Effort/reward imbalance and self-reported job stress did not seem to have a significant influence on this biomarker. A regression analysis revealed that vitality and decision authority, together with coffee consumption and coping strategies, accounted for 22.2% of the variance in evening cortisol levels (Harris et al. 2007).

In a trial aiming to evaluate the potential effectiveness of behavioural/psychoeducational training on chronic occupational stress, Nickel et al. found that the training resulted in lowering cortisol levels, comparing post-intervention results with both the baseline ($p < 0.001$ upon awakening and 15, 30, and 60 min after awakening) and the control group. The intervention also resulted in a significant improvement of QoL scores (SF-36—$p < 0.05$), with the only exception of the physical functioning domain (Nickel et al. 2007)

Instead, in a group of professional jockeys, Poon et al. did not report any difference in blood cortisol levels and QoL scores (WHOQOL-bref) in comparison with a control group of healthy students (Poon et al. 2018).

Rector et al. grouped the professionally active epidemiological sample according to the prevalence of CMV infection. Neither cortisol levels, either considered as daily cortisol output (AUC) or cortisol awakening response (CAR), nor CRP were reported to be associated with CMV infection or reactivation (CMV-IgG) (Rector et al. 2014)

In a study involving hotel housekeepers, Rosemberg et al. reported relatively poor physical and mental health (SF-12) scores, with 38% and 39% of participants scoring below the US population, respectively. Six participants (12.2%) had cortisol levels higher than the clinical cut-off point (>23 ug/dL). The Allostatic Load Index (CRP, High-Density Lipoprotein (HDL), waist/hip ratio (WHR), Body Mass Index (BMI), Hemoglobin A1c (HbA1c), cortisol, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Heart Rate (HR)) resulted in being associated with high job strain ($p = 0.011$), while no correlation has been found with physical and mental health (SF-12) (Rosemberg et al. 2019).

On the contrary, Sadowska et al. did not find any difference in cortisol levels between caregivers and the control group (Sadowska et al. 2021).

An N-to-1 study involving a patrol police officer followed for 3 weeks, revealed a typical daily salivary cortisol pattern, characterised by overall high levels and a flattened cortisol awakening response. The QoL scores (SF-36), measured at the beginning of the study, were on average, with the lower score associated with vitality (Giessing et al. 2020).

2.2.6.4. Stress Biomarkers – Autonomic Nervous System Activity (a-Amylase)

Contrary to what was reported for cortisol, the trial reported by Feicht et al. using the web-based happiness training revealed a significant reduction in the α-amylase morning activity at the end of the study ($p = 0.002$) (Feicht et al. 2013).

According to the results on salivary cortisol, Giessing et al. reported a daytime salivary concentration of α-amylase higher than those found in the literature for high-stress populations (Giessing et al. 2020).

2.2.6.5. Circadian Cycle – Melatonin

Vlahoyiannis et al. investigated the role of work schedule in a sample of nurses, comparing those with a fixed morning shift (07:00 AM–03:00 PM) with those working rotating shifts. Nurses in this last group reported QoL scores (SF-36) significantly lower than their colleagues with a fixed morning shift ($p = 0.010$), specifically in the physical functioning and general health domains ($p = 0.006$ and $p = 0.010$, respectively). No differences were found in the salivary melatonin concentration, either in morning or evening sampling (Vlahoyiannis et al. 2022).

2.3. Discussion

In recent years, the assessment of working conditions effects on workers' health was enriched by the increasing importance tributed to the investigation of the consequences to adverse psychosocial working environments (Siegrist and Li 2017).

Even if investigating simultaneously the eventual alterations attributable to chronic stress in both self-reported well-being and molecular pathways could be particularly valuable in the promotion of workers' health (Chandola and Zhang 2018), this approach turned out to be uncommon and the accurate statistical analysis of their mutual relationship even rarer. Specifically, investigating the alterations in biomarkers associated with the onset of clinical outcomes, even in the absence of symptoms, might be critical in the early identification of workers at higher risk of health impairment in the future (Ebata, Tatsuta, and Tatemichi 2017). Matching these data with self-rated health measurements, which have been proposed as an early predictor of mortality (Singh-Manoux et al. 2007), would be thus interesting at different levels: (i) in populations including young and healthy subjects not experiencing the most common morbidity risk factors and inflammatory-related comorbidities (Gill et al. 2014), (ii) in the general workforce to assess the role of workforce ageing in mediating these alterations (Jordakieva et al. 2022), (iii) in professionals trained to deal with high-stress situations, in which the personal response to working conditions might be altered (Giessing et al. 2020). The review highlighted a huge heterogeneity in the investigation of both the QoL and the bio-molecular profile, making it difficult to identify a "golden standard" assessment protocol, and a general lack of details concerning the working context and work-related factors, preventing to obtain results valid for the general, professionally active population.

Workers required to complete physically and psychologically demanding tasks for extended periods and to make difficult decisions, as workers employed in healthcare and emergency departments, police officers, and military personnel are at a higher risk of occupational stress, physical injuries, and psychological outcomes, such as major depression and post-traumatic stress disorder (Wild et al. 2016; Corrigan et al. 2021). Their distinctive working conditions and duties may exacerbate the role of physical, physiological, cognitive, and psychological stressors they have to cope with (Corrigan et al. 2021), highlighting the relevance of prevention, screening, and treatment strategies (Pietrzak et al. 2014) and the reduced efficacy of approaches based only on interventions offered after the exposure to traumatic events (Wild et al. 2018).

Not surprisingly, fourteen of the twenty-three papers included active-duty military personnel and veterans (Devoto et al. 2017; Kanefsky et al. 2019; Heinzelmann et al. 2014; Gill et al. 2014), community health agents (Knuth et al. 2016), sworn officers and patrol police officers (Everding et al. 2016; Giessing et al. 2020), health care professionals (Ebata, Tatsuta, and Tatemichi 2017; Harris et al. 2007; Jordakieva et al. 2022; Kasemy et al. 2020; Ozyurek et al. 2021; Vlahoyiannis et al. 2022) and caregivers (Sadowska et al. 2021). A further critical issue involving these professionals is the presence of shift work, which has a significant impact on workers' health, QoL, and well-being (Vlahoyiannis et al. 2022).

The research engaging active-duty military personnel and veterans, representing a half of those included in the "clinical" group (Devoto et al. 2017; Gill et al. 2013; Heinzelmann et al. 2014; Kanefsky et al. 2019), investigated the alterations in inflammatory status and QoL in subjects suffering from depression, PTSD, and TBI. The peculiar portrait obtained might be more likely related to their physical and psychiatric conditions, which could be, in turn, a consequence of distinctive working conditions and requirements. Veterans represent indeed a group needing particular attention in terms of QoL and well-being promotion, and in which the onset of chronic inflammation is a common outcome (Gill et al. 2014). The investigation on risk factors triggering the later onset of health issues pointed out in these researches and the implementation of preventing strategies to eliminate or, at least, attenuate them could lead to the definition of valuable and efficient interventions which could be extended to all the working population. The ultimate goal should be the understanding of how work-related factors and working conditions could affect physiological pathways to identify the most susceptible groups in a window of opportunity where subclinical hallmarks of chronic inflammation may still be reversible. A valid array of indicators sensitive to both the derangements from physiological conditions and their restoring due to stress reduction, would be necessary to investigate the effectiveness of interventions attempting to promote workers' health and safety and, eventually, to address occupational health disparities (Rosemberg et al. 2019).

The stress response is a complex mechanism occurring whenever there is a discrepancy between expectation and reality, involving the activation of several inter-dependent pathways, including behavioural, autonomic, endocrine, and immune systems (Harris et al. 2007). Maintaining these mechanisms constantly activated, as resulting from the absence of match between job requirements and workers' capabilities, may result detrimental to health and well-being (Herman 2013). In the article included in the review, the biological markers assessed represent three main biological pathways: neuroendocrine activation, oxidative stress, and inflammation.

In the clinical population, the blood cortisol level was higher in community health agents with less than one year of service and negatively correlated with QoL, probably due to the redistribution of energy to cope with the new experiences (Knuth et al. 2016). A general increase in cortisol/ACTH response was observed after the administration of corticotropin-releasing hormone in relation to work-related stress, similarly as in patients suffering for major depression (Sandström et al. 2011). In the non-clinical population, the administration of behavioural training programs seems to be effective in enhancing both the health-related QoL and the bio-molecular profile

(Sandström et al. 2011). Specifically, the employment of a web-based training was efficient in improving the QoL scores and in decreasing the morning α-amylase in employees operating in an insurance company, possibly revealing a tendency to start the day in a less "stressed" way (Feicht et al. 2013). Behavioural/psychoeducational training could as well reduce limitations due to bodily pain and physical health, improving the perceptions of factors related to health and emotional domains able to interfere with work and daily activities (Nickel et al. 2007). The early identification of subjects needing support beyond conventional care and the sensibilisation of adopting healthier lifestyles can thus play a key role in the workers' well-being promotion (Nickel et al. 2007; Sudheeran et al. 2016).

Concerning oxidative stress and inflammation, IL-6 was associated with lower HRQOL scores in PTSD patients (Gill et al. 2013) and with symptoms of mental distress, such as depression, fatigue, disturbed sleep, sleep restriction, and cognitive impairment (Heinzelmann et al. 2014; Maes et al. 2012). The association between chronic inflammation and HRQOL in active-duty military personnel in suffering for PTSD and depression, reveal that the administration of effective treatments and/or intervention can represent an effective strategy to reduce morbidity risks in ageing veterans (Gill et al. 2014). Indeed, elevated blood IL-6 concentration in young military personnel might be predictive of morbidity and mortality risk factors' development in later years (Gill et al. 2014). Sleep restoration programs, for example, seem effective in reducing inflammation (in contrast of insomnia, enhancing the circulatingiL-6 concentration) and in improving health and well-being, allowing the avoidance of subsequent onset of inflammatory-related risk factors, especially in young populations (Heinzelmann et al. 2014). The investigation of the subclinical reactivation of CMV infection revealed an association between psychological stress and CMV-IgG concentration in the CMV+ group, with low mental health associated with an increase in CMV-IgG and not with being infected *per se*. The stronger association was reported in low socio-economic status (SES) employees (job status and education), while virtually absent in high-SES workers, maybe as consequence to be exposed to stressors whose effects could not be balanced by coping resources, leading to an allostatic load condition (Rector et al. 2014).

In conclusion, the review highlights some critical issues in addressing the topic and the importance of further investigating the relationship between the QoL and the bio-molecular profile. These results could help in the definition of efficient strategies of workers' health and well-being promotion. To reach this goal, the development of a valid array of biomarkers sensitive to both derangements from physiological conditions and stress reduction in a non-invasive way would be fundamental, especially to identify those groups at higher risk of health outcomes.

3. Experimental Projects

3.1. Study Lines

The experimental part of the project can be split in three study lines according to the different aims, epidemiological samples, and methodologies employed. The aim of the present project is to analyse the possible relationship between bio-molecular measurement and QoL evaluations to provide some useful tools for an objective assessment and promotion of QoL in different populations.

- *Study Line n. 1: Easy Work Project*
- *Study Line n. 2: Health Promotion in Working Environment*
- *Study Line n. 3: Health Promotion during Pregnancy*

The Study Lines n. 1 and 2 aim to investigate the working environments, while the Study Line n. 3 is declined in the life environment.

3.2. Working Environment

3.2.1. Study Line 1: Easy Work Project

3.2.1.1. Aim

The aim of the Study Line n. 1 is to evaluate the role of the web-based administration of moderate PA in a working setting during the COVID-19 pandemic in 2021. The efficacy of the intervention would be observed in terms of modulation of the QoL and of the bio-molecular profile. This with the ultimate intention of define useful approaches to be implemented in programs promoting the workers' health and well-being, with a special attention to those working from home.

3.2.1.2. Material and methods

3.2.1.2.1. Study design

Measurements were performed at the beginning of the study, to assess the baseline values (March 2021 – T0), after three months of PA administration (June 2021 – T1), and at the end of the summer (September 2021 – T2). Each subject, after agreeing to participate signing out a written informed consent form, filled out a questionnaire, underwent the assessment of anthropometric measurements, and provided a spot urine sample for the biomarkers' quantification. Data and samples were pseudonymisated immediately after collection assigning an alphanumerical string to each subject.

3.2.1.2.2. Epidemiological Sample and Recruitment

The participation to the project was extended to all the workers employed in a Company involved in the information technology sector (n = 51) located in Piedmont region (North-West Italy), regardless of their sex, age, and task. Each volunteer received a detailed description of the project and signed up a written informed consent form. The study was approved by the University of Turin ethics committee (Prot. N. 335619, 22.07.2020) and was in line with the ethical standards reported in The Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013).

3.2.1.2.3. Questionnaire

Each subject filled out a comprehensive questionnaire covering a broad range of factors, including demographic variables (sex, age), concern for the pandemic, lifestyle (smoking status and physical activity intensity level), and habits (smoking status, PA and food frequency (number of times/weeks each subject eats fruits and vegetables, red meat, and fish), QoL. The questionnaire was self-administered by the Lime Survey platform (2012, Hamburg, Germany) and the link was made available on the sampling day.

3.2.1.2.3.1. WHOQOL-bref

The Italian version of the World Health Organisation Questionnaire – Bref version (Girolamo et al. 2000) was considered the election choice. The scale consists of 26 items referring to the last

15 days, evaluating the QOL in four domains: i) physical health, ii) psychological, iii) social relationships, and iv) environmental, with a 5-point Lickert response scale. An additional domain (overall) could be obtained combining the scores of the first two answers. The score of each domain ranges between 0 and 20, with higher values revealing a better QOL in that area. The Cronbach's α was > 0.7 for all domains, except for the social relationship domain.

3.2.1.2.3.2. Healthy Days

Additionally, in *Study Line 1* and *2*, we administered the 3 questions of the 4-item set of Healthy Days (HD) core questions (CDC HRQOL– 4) (Taylor 2000) concerning physical health, mental health, and activity limitation reference respondents' health during the previous 30 days (Shockey, Zack, and Sussell 2017). The overall measurement can be obtained combining the number of Healthy Days concerning physical and psychological health. Consistently with previous research, we chose a 14-day cut point to discriminate frequent physical and psychological distress and frequent activity limitation (Shockey, Zack, and Sussell 2017; Strine et al. 2004).

3.2.1.2.3.3. International Physical Activity Questionnaire (IPAQ)

The PA level was evaluated by the Italian version of the International Physical Activity Questionnaire - Short Form (IPAQ-SF) (Minetto et al. 2018). The scale comprises 7 items recording the frequency and the duration of activities of four intensity levels in the last 7 days: i) vigorous-intensity activities, ii) moderate-intensity activities, iii) walking, and iv) sitting. The energy expenditure from those activities (expressed in Metabolic Equivalent Task (MET)*min/week) was estimated as the n. of days spent in the activity × average duration of the activity *per* day × energy cost of the activity. According to these values, the physical activity levels of each subject were defined as "Low" – "Medium" – "High" (Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)—short and long forms. https://sites.google.com/site/theipaq/, accessed 23.09.2022).

3.2.1.2.4. Bio-molecular Profile assessment

The bio-molecular profile was assessed in spot urine samples collected during the sampling day, kept refrigerated, aliquoted and stored at −80°C until analysis.

3.2.1.2.4.1. 15-F2t-Isoprostane

15-F_{2t}-IsoP urinary concentration was quantified by competitive E.L.I.S.A. kit (Urinary Isoprostane ELISA Kit, Oxford Biomedical Research, MI, USA), according to the manufacturer's instructions. In this assay, the 15-F_{2t}-IsoP in samples or standards competes with 15-F_{2t}-IsoP conjugated to horseradish peroxidase (HRP) for binding to a polyclonal specific antibody coated on the microplate. The substrate addition enhances the HRP activity resulting in colour development, which intensity is inversely proportional to the amount of unconjugated 15-F_{2t}-IsoP in samples or standards. The assay Limit of Detection (LOD) was 0.08 ng/mL.
Thawed samples (100 µL) were transferred into clean Eppendorf with 5 µL of β-glucuronidase, vortexed and then incubated 2 h at 37 °C. At the end, samples were diluted 1:4 with the Enhanced Dilution Buffer (EDB) to eliminate interferences due to non-specific bindings. An eight-point standard curve was prepared from 1 µg/mL 15-F_{2t}-IsoP Standard stock solution diluted with EDB (S7: 100 ng/mL; S6: 50 ng/mL; S5: 10 ng/mL; S4: 5 ng/mL; S3: 1 ng/mL; S2: 0.1 ng/mL; S1: 0.05 ng/mL;

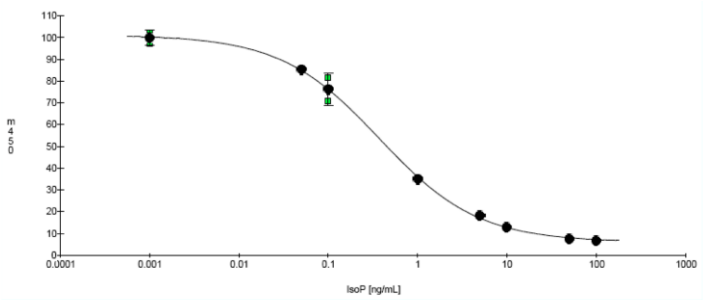
B0: 0 ng/mL). 100 µL of Standards or samples were then added in the 96-well coated microplate following the following scheme (**Figure 6**):

	1	2	3	4	5	6	7	8	9	10	11	12
A	S_7	S_7	U_1	U_1	U_9	U_9	U_{17}	U_{17}	U_{25}	U_{25}	U_{33}	U_{33}
B	S_6	S_6	U_2	U_2	U_{10}	U_{10}	U_{18}	U_{18}	U_{26}	U_{26}	U_{34}	U_{34}
C	S_5	S_5	U_3	U_3	U_{11}	U_{11}	U_{19}	U_{19}	U_{27}	U_{27}	U_{35}	U_{35}
D	S_4	S_4	U_4	U_4	U_{12}	U_{12}	U_{20}	U_{20}	U_{28}	U_{28}	U_{36}	U_{36}
E	S_3	S_3	U_5	U_5	U_{13}	U_{13}	U_{21}	U_{21}	U_{29}	U_{29}	U_{37}	U_{37}
F	S_2	S_2	U_6	U_6	U_{14}	U_{14}	U_{22}	U_{22}	U_{30}	U_{30}	U_{38}	U_{38}
G	S_1	S_1	U_7	U_7	U_{15}	U_{15}	U_{23}	U_{23}	U_{31}	U_{31}	U_{39}	U_{39}
H	B_0	B_0	U_8	U_8	U_{16}	U_{16}	U_{24}	U_{24}	U_{32}	U_{32}	RB	RB

Figure 6: Plate scheme of Standards, Samples, and Blanks position

Then 100 µL of 15-F2t-IsoP HRP Conjugate (diluted 1:50 with EDB) was added to each well omitting the Reagent Blank (RB), whose wells were filled with 100 µL of EDB. After 2h of incubation at room temperature, the plate was washed three times. Each wash consisted in removing the plate content by inversion of the plate, tapping out the remaining content on a lint free paper towel, adding 300 µL of 1x Wash Buffer (diluted with deionised water), and letting the plate stand for 2-3 minutes. At the end, the plate content was removed, each well was filled with 200 µL of TMB Substrate and the plate was incubated for 20 - 40 minutes, until an appreciable blue hue could be observed in B0 wells. At the end, 50 µL of 3 M Sulfuric Acid were dispensed to each well to stop the reaction, causing a colour change from blue to yellow. The plate was then read at 450 nm.

To calculate the 15-F2t-IsoP in samples, the RB absorbance values were averaged and subtracted by the values of all the other wells. Standard duplicates were averaged, and each value was then divided by the mean of B0 values and multiplied by 100 to obtain the %B0 values. The standard curve graph was created plotting the %B0 values (y-axes, linear) vs standard concentration (x-axis, logarithmic), as the one reported in **Figure 7**. The concentration of each unknown sample was then calculated from the corresponding %B0 value, accounting for the proper dilution factor.



Typical B/B$_0$: 20% - 3.5 ng/mL; 50% - 0.45 ng/mL; 80% - 0.08 ng/mL

Figure 7: Typical 15-F2t-IsoP standard curve

3.2.1.2.4.2. Thiobarbituric Reactive Substances

MDA urinary concentration was quantified by colorimetric technique (Colorimetric Microplate Assay for 2-Thiobarbituric Acid Reactive Substances (TBARS), Oxford Biomedical Research, MI, USA), according to the manufacturer's instructions. The 2-Thiobarbituric Acid Reactive Substances (TBARS) assay is based on the quantification of the MDA-TBA adduct formed by MDA and TBA under high temperature and acidic conditions. A Knoevenagel-type condensation between

one molecule of MDA and 2 molecules of 2-thiobarbituric acid leads to the formation of a chromophore with absorbance maximum at 530–540 nm. The interference of coloured compounds naturally present in urine specimens can be removed by running a sample blank for each sample.
An 8-point standard curve was prepared as reported in **Figure 8** from a 20 µM MDA Standard Stock solution of malondialdehyde tetrabutylammonium (MDA-TBA) salt in a slightly basic buffer, to overcome the MDA instability. When mixed with the acidic Indicator Solution, the MDA-TBA molecule the acidification generates MDA quantitatively. The 20 µM MDA Standard Stock was prepared diluting the 10 mM MDA Standard 1:500 in dH_2O immediately prior to use.

Standard	MDA Conc. (μM)	Vol. of dH_2O (μL)	Vol. of 20 μM MDA Stock (μL)
S_0	0	400	-
S_1	0.5	390	10
S_2	1.0	380	20
S_3	2.5	350	50
S_4	5.0	300	100
S_5	10.0	200	200
S_6	15.0	100	300
S_7	20.0	-	400

Figure 8: Colorimetric Standard Curve preparation

To quantify of Total MDA in Standards and Samples, the following reagents were added into microcentrifuge tubes and mixed well:

- Standards: 200 µL of standards and 200 µL of Indicator Solution;
- Samples: 200 µL of sample and 200 µL of Indicator Solution;
- Blanks: 200 µL of sample and 200 µL of Acid Reagents.

Standards, Samples, and Blanks were incubated at 65°C for 45 minutes and then 150 µL of each solution was added to the microplate as reported in **Figure 9** and read at 532 nm.

	1	2	3	4	5	6	7	8	9	10	11	12
A	S_0	S_0	SPL_1	SPL_1	SPL_5	SPL_5	SPL_9	SPL_9	SPL_{13}	SPL_{13}	SPL_{17}	SPL_{17}
B	S_1	S_1	SB_1	SB_1	SB_5	SB_5	SB_9	SB_9	SB_{13}	SB_{13}	SB_{17}	SB_{17}
C	S_2	S_2	SPL_2	SPL_2	SPL_6	SPL_6	SPL_{10}	SPL_{10}	SPL_{14}	SPL_{14}	SPL_{18}	SPL_{18}
D	S_3	S_3	SB_2	SB_2	SB_6	SB_6	SB_{10}	SB_{10}	SB_{14}	SB_{14}	SB_{18}	SB_{18}
E	S_4	S_4	SPL_3	SPL_3	SPL_7	SPL_7	SPL_{11}	SPL_{11}	SPL_{15}	SPL_{15}	SPL_{19}	SPL_{19}
F	S_5	S_5	SB_3	SB_3	SB_7	SB_7	SB_{11}	SB_{11}	SB_{15}	SB_{15}	SB_{19}	SB_{19}
G	S_6	S_6	SPL_4	SPL_4	SPL_8	SPL_8	SPL_{12}	SPL_{12}	SPL_{16}	SPL_{16}	SPL_{20}	SPL_{20}
H	S_7	S_7	SB_4	SB_4	SB_8	SB_8	SB_{12}	SB_{12}	SB_{16}	SB_{16}	SB_{20}	SB_{20}

Figure 9: Plate disposition layout

To quantify the MDA in samples, the optical density (OD) corresponding to all duplicate wells were averaged. The Standard Curve was plotted using the OD vs the MDA concentration of each standard and a linear fit method was employed to obtain the equation of the line (**Figure 10**). Then, for each specimen, the OD of the blank was subtracted from the OD of the sample and the MDA content was obtained by the Standard Curve equation. The declared LOD is 1.0 µM.

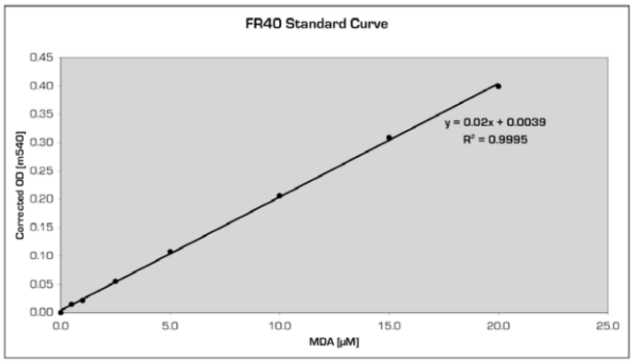


Figure 10: Typical Standard Curve

3.2.1.2.4.3. Total Antioxidant Power

The Total Antioxidant Power (TAP) was measured by a colorimetric assay (Colorimetric Microplate Assay for Total Antioxidant Power, Oxford Biomedical Research, MI, USA), according to the manufacturer's instructions. The aim of the assay is to provide a total measure of the antioxidant power, despite the multiple pathways and the influences of lifestyle and nutritional supplements on the individual's antioxidant capacity.

The assay consists in the conversion of Cu+2 to Cu+1 due to the reduction potential of standard or samples, determining an alteration in the ion's absorption characteristics. The Cu+1 is able to bind the chromogenic reagent in a stable 2:1 complex with a maximum absorption at 450 nm. The calibration curve is created starting form a known concentration of Trolox and data were expressed in mM Trolox equivalents or µM copper reducing equivalents.

A 5-point standar curve was prepared according to the following scheme (**Figure 11**) from a Trolox standard reconstituted with 2 mL of Ethanol and vortexed 30-60 seconds.

Standard	Trolox Conc. (mM)	Vol. of Deionized Water (μL)	Transfer Volume (μL)	Transfer Source	Final Volume (μL)
S_5	2.0	-	2000	2 mM Stock	1500
S_4	1.0	500	500	S_5	500
S_3	0.5	500	500	S_4	500
S_2	0.25	500	500	S_3	500
S_1	0.125	500	500	S_2	1000
S_0	0	500	-	-	500

Figure 11: Standard Curve preparation

Thawed urine samples were diluted 1:4 with pH 7.0 PBS prior to assay. Then standard and samples were diluted 1:40 with the Dilution Buffer provided (15 µL sample and 585 µL Dilution Buffer) and 200 µL of Samples or Standards were placed in the plate according to the scheme in **Figure 12**, adding Dilution Buffer in the Reagent Blank (BLK) wells.

The plate was read at 450 nm to obtain a reference measurement. Then, each well was filled with 50 µL of Copper solution and, after 3 minutes of incubation at room temperature, 50 µL of Stop solution. The plate was newly read at 540 nm.

The net absorbance was obtained by subtracting the reference reading from the end reading, and then the values concerning the standard (y-axis) were plotted against the respective Trolox concentration (x-axis), obtaining a typical standard curve.

	1	2	3	4	5	6	7	8	9	10	11	12
A	S_0	S_0	U_3	U_3	U_{11}	U_{11}	U_{19}	U_{19}	U_{27}	U_{27}	U_{35}	U_{35}
B	S_1	S_1	U_4	U_4	U_{12}	U_{12}	U_{20}	U_{20}	U_{28}	U_{28}	U_{36}	U_{36}
C	S_2	S_2	U_5	U_5	U_{13}	U_{13}	U_{21}	U_{21}	U_{29}	U_{29}	U_{37}	U_{37}
D	S_3	S_3	U_6	U_6	U_{14}	U_{14}	U_{22}	U_{22}	U_{30}	U_{30}	U_{38}	U_{38}
E	S_4	S_4	U_7	U_7	U_{15}	U_{15}	U_{23}	U_{23}	U_{31}	U_{31}	U_{39}	U_{39}
F	S_5	S_5	U_8	U_8	U_{16}	U_{16}	U_{24}	U_{24}	U_{32}	U_{32}	U_{40}	U_{40}
G	U_1	U_1	U_9	U_9	U_{17}	U_{17}	U_{25}	U_{25}	U_{33}	U_{33}	U_{41}	U_{41}
H	U_2	U_2	U_{10}	U_{10}	U_{18}	U_{18}	U_{26}	U_{26}	U_{34}	U_{34}	BLK	BLK

Figure 12: Plate disposition layout

The TAP concentration in each sample can be expressed in µM Trolox eqiuivalents solving the standard. Curve equation: $y = mx + q$.

3.2.1.2.4.4. Interleukin 6

In *Study Line 1* the urinary concentration of IL-6 was measured by a High Sensibility quantitative sandwich ELISA kit (Quantikine® HS ELISA, HS600C, R&D, MN, USA) according to manufacturers' instructions. The assay contains *E. coli*-expressed recombinant human IL-6 and measures the colour development in proportion to the IL-6 amount in samples.

A 7-point standard curve (diluted with the Calibrator Diluent – **Figure 13**) was prepared from the Human IL-6 HS Standard, reconstituted with 1 mL of milli-Q water to obtain a stock solution of 100 pg/mL and sit for a minimum of 15 minutes with a gentle agitation. Each tube was mixed well until proceeding to the next transfer.

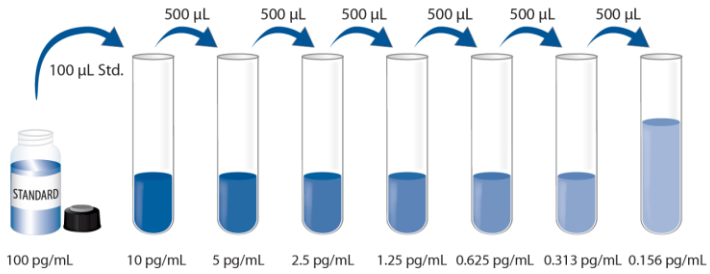


Figure 13: Standard curve preparation

Each well of the microplate was filled with 100 µL of Assay Diluent RD1W and 100 µL of standard, control, or samples. The plate was sealed and incubated 2h at room temperature on a horizontal orbital microplate shaker at 500 ± 50 rpm.

Wells were then aspirated and washed filling them with 400 µL of Wash Buffer (40 mL of Wash Buffer Concentrate diluted with 960mL of milli-Q water) using a squirt bottle. The washing procedure was repeated for a total of four washes, carefully completely removing the liquid at the end of each step. At the end, the plate was inverted and blotted against a clean paper towel. Each well was now filled with 200 µL of Human IL-6 conjugate, then the plate was sealed and incubated 1 h at room temperature on the shaker, before repeating the washing procedure. At the end, 200 µL of Streptavidin Polymer-HRP (1X obtained mixing 0.215 mL of Streptavidin Polymer-HRP (100X) to the Streptavidin Polymer-HRP Diluent) were added to each well, and the plated was incubated for 30 minutes, before being washed again. Then, each well was filled with 200 µL of Substrate Solution (obtained mixing up Colour Reagents A and B in equal volumes within 15 minutes of use), and the plate was newly incubated at room temperature on the benchtop in the dark. 50 µL of Stop

Solution were added, obtaining a colour change form blue to yellow. The plate was gently tapped to ensure the reagent mixing. The optical density was measured within 30 minutes at 450 nm and at 540 nm. The 540 nm reading was then subtracted from the one at 450 nm, to correct eventual optical imperfections of the microplate.

The duplicates of each standard, control, and sample were then averaged and the averaged zero standard optical density was subtracted from each of them. The standard curve was calculated by a software able to generate a four-parameter logistic curve-fit (https://mycurvefit.com). The declared LOD of the assay is 0.031 pg/mL.

3.2.1.2.4.5. Interleukin 10

In *Study Line 1* the urinary concentration of IL-10 was quantified by the *Human IL-10 ELISA Kit* (EHIL10, Thermo Fisher Scientific – Invitrogen, MA, USA) according to the manufacturer's instructions. The assay sensitivity declared was <3pg/mL.

A six-point standard curve was obtained preparing a 1:2.5 serial dilution from the Recombinant Human IL-10 Standard (**Figure 14**), previously reconstituted with ultrapure water within 1h of the use and gently mixed inverting the vial. The Standard Diluent was employed for dilutions.

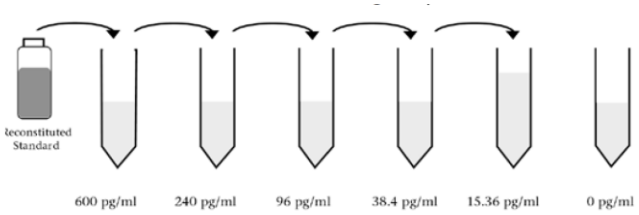


Figure 14: Standard curve preparation

Wells were filled with 50 µL of standard or samples in duplicate and 50 µL of Biotinylated Antibody Reagent. Wells not containing standards or samples were filled with 50 µL of Standard Diluent (controls). The plate was sealed and incubated 2h at room temperature. At the end the plate was emptied and washed vigorously filling each well with the Wash Buffer (50 mL of 30X Wash Buffer were previously diluted with 1.5 L of ultrapure water and mixed thoroughly) by a squirt bottle and newly emptied. The procedure was repeated two more times for a total of three times. The plate was then blotted onto a paper towel. 100 µL streptavidin-HRP Solution (30 µL of Streptavidin-HRP Concentrate added to 12 mL of Streptavidin-HRP Dilution Buffer and gently mixed) were then added to each well, the plate was sealed and incubated for 30 minutes at room temperature. At the end the plate content was discarded, and the plate was washed as previously described. Each well was filled with 100 µL of TMB Substrate Solution and the plated was incubated not sealed in the dark for 30 minutes to allow the development of the enzymatic reaction. At the end, the addition of 100 µL of Stop Solution allow the stop of the reaction and determined the colour change, from blue to yellow. The plate was then read within 30 min at 450 nm and 550 nm. The 550nm reading was subtracted from the 450nm one to correct for optical imperfections of the microplate.

The standard curve graph was then obtained creating the average absorbance of each standard (y-axis) vs the corresponding IL-10 standard concentration (pg/mL – x-axis). The IL-10 amounts in each sample was then calculated interpolating the respective absorbance values in the equation obtained from the standard curve graph. Absorbance values obtained for duplicates should be within the 10% of the mean values.

3.2.1.2.5. Physical Activity Administration Protocols

The administration was web-based, to deal with both pandemic restrictions and maximise the compliance of volunteers taking part to the project.

The administration of PA started on the 12th of April 2021. Due to the restrictions in force in Italy to combat the spread of the pandemic, the lessons of PA were delivered remotely, via web meeting, by a skilled trainer. Each subject was proposed to participate in two 1-hour weekly sessions, for a total of 23 sessions, at the end of the working day (between 18.00 and 20.30) from their homes.

Each lesson was organised as follows: i) general warm-up exercises (10-15 min), ii) warm-up specific for the later activities (10-15 min), iii) metabolic exercises, aerobic ac-tivities, metabolic training, full-body strength workout, posture exercises, balance and flexibility exercises (15-25 min), iv) stretching and cool-down exercises (10 min).

Each participant was also recommended to complete the weekly training with 30-40 min of unsupervised outdoor fit walking.

3.2.1.2.6. Statistical analysis

Statistical analyses were performed by SPSS Statistics 28 (IBM SPSS Statistics, New York, NY, USA). Graphs were created by R Studio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA).

Categorical variables have been reported as frequency (n) and percent (%) and compared by the χ squarewd test, while continuous variables have been reported as median and interquartile range (IQR). Wilcoxon's Signed-Rank Test or Kruskal-Wallis test were employed to compare ordinal data and continuous variables. The Cronbach α was calculated for WHOQOL-bref questionanires and for work-related factors scales (Workload, Exhaustion, Job Insecurity and Job Autonomy).

Specifically, measurements of TBARS under the limit of detection (LOD) have been calculated as LOD/2. Due to the small number of subjects, the analyses have been conducted with non-parametric tests. Specifically, between the beginning and at the end of the intervention (T0 vs T1) and data between the end of the intervention and the end of the following 3-month period with no longer PA administration training (T1 vs T2). To overcome the absence of a control group, we re-run analyses splitting the epidemio-logical sample in two groups, who took part to <60% and >60% of PA lessons, respectively. The significance level of the tests was 0.05.

3.2.1.3. Results

Table 4, **Table 5**, **Table 6**, and **Table 7** in summarise the characteristics of workers involved in the study, obtained by the answers to questionnaires and biological analyses. Eight subjects followed less than the 60% of the training lessons.

	n (%)
Sex	
M	19 (73.1%)
F	7 (26.9%)
	Mean ± SD
Age (yr.)	43.15 ± 11.85

Table 4a: Demographic characteristics of the epidemiological sample

	T_0	T_1	T_2	T_0 *vs* T_1	T_0 *vs* T_2
	n (%)				
Working years					
0 – 5 yrs.	8 (30.8%)				
5 – 10 yrs.	3 (11.5%)				
10 – 15 yrs.	3 (11.5%)				
15 – 20 yrs.	7 (26.9%)				
> 20 yrs.	5 (19.2%)				
Physical Activity level					
Low	7 (26.9%)				
Moderate	11 (42.3%)				
High	8 (30.8%)				
	n (%)	*n (%)*	*n (%)*		
Concern for the pandemic					
None	0 (0%)	4 (16.7%)	2 (8.7%)	**0.009**	0.782
Very mild	5 (19.2%)	7 (29.2%)	7 (30.4%)		
Mild	10 (38.5%)	6 (25.0%)	7 (30.4%)		
Moderate	8 (30.8%)	6 (25.0%)	6 (26.1%)		
Severe	3 (11.5%)	1 (4.2%)	1 (4.3%)		
Vegetable and fruit consumption (n. of times/week)					
1 – 2	2 (7.7%)	1 (4.0%)	0 (0.0%)	0.317	0.564
3 – 4	2 (7.7%)	3 (12.0%)	3 (13.0%)		
≥ 5	22 (84.6%)	21 (84.0%)	20 (87.0%)		
Read meat consumption (n. of times/week)					
None	0 (0%)	1 (4.0%)	0 (0.0%)	**0.046**	0.317
1 – 2	18 (69.2%)	19 (76.0%)	18 (78.3%)		
3 – 4	8 (30.8%)	5 (20.0%)	5 (21.7%)		
≥ 5	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Fish consumption (n. of times/week)					
None	4 (15,4%)	2 (8.0%)	2 (8.7%)	0.157	0.317
1 – 2	21 (80.8%)	22 (88.0%)	20 (87.0%)		
3 – 4	1 (3.8%)	1 (4.0%)	1 (4.3%)		
≥ 5	0 (0%)	0 (0%)	0 (0%)		
Sleep (h/night)					
< 6	5 (19.2%)	4 (16.0%)	3 (13.0%)	0.317	1.000
≥ 6	21 (80.8%)	21 (84.0%)	20 (87.0%)		

Table 4b: Basic characteristics of the epidemiological sample

	T0	T1	T2	T0 *vs* T1	T1 *vs* T2	T0 *vs* T2
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p-value*	*p-value*	*p-value*
Quality of Life (QOL)						
WHOQOL-brief – physical domain	16.00 (3.00) [a]	16.00 (3.37) [b]	16.57 (4.00) [d]	0.760	**0.034**	0.600
WHOQOL-brief – psychological domain	14.33 (3.33) [a]	14.00 (3.00) [b]	14.67 (2.66) [d]	**0.010**	0.880	**0.002**
WHOQOL-brief – social relationship domain	14.67 (4.00) [a]	14.67 (3.33) [b]	14.67 (4.00) [d]	0.674	0.142	0.342
WHOQOL-brief – environmental domain	15.00 (2.13) [a]	15.00 (3.00) [b]	15.00 (2.00) [d]	0.134	0.981	0.345
Healthy Days – physical aspect	29 (2) [a]	29 (3) [b]	30 (2) [d]	0.885	0.384	0.487
Healthy Days – psychological aspect	27.5 (5) [a]	28 (5) [b]	29 (3) [d]	0.715	**0.014**	**0.011**
Healthy Days – usual activities	30 (0) [a]	30 (3) [b]	30 (1) [d]	0.278	0.065	0.673
Healthy Days – total	27 (5.50) [a]	26 (7) [b]	28 (4) [d]	0.984	**0.012**	**0.038**
BMI	25.50 (6.09) [a]	25.00 (6.05) [b]	25.28 (5.57) [d]	**0.002**	0.131	0.075
Biomarkers						
15-F_{2t}-IsoP [ng/mg crea]	3.55 (1.90) b *	2.64 (0.91) a	2.67 (1.39) d	**< 0.001**	0.064	**0.005**
TBARS [µmol MDA/mmol crea]	0.08 (0.06) a*	0.05 (0.08) a	0.06 (0.10) d	0.326	0.144	0.935
TAP [mmol Trolox eq./mmol crea]	0.46 (0.19) a	0.37 (0.16) a	0.46 (0.15) d	**0.004**	**0.029**	0.574
IL-6 [pg/mg crea]	1.49 (1.47) a	1.17 (0.85) a	1.09 (1.11) d	**0.012**	0.605	0.125
IL-10 [pg/mg crea]	1.49 (4.78) a	0.72 (1.05) c	0.94 (2.07) d	**0.018**	0.808	**0.019**

Table 5: Comparisons among the three sampling points concerning QoL, BMI and biomarkers in the whole participants' group. [a]26 subjects; [b]25 subjects; [c]24 subjects; [d]23 subjects; [e]22 subjects; [f]20 subjects; *an outlier value has been removed. *IQR = Inter-Quartile Range; 15-F-2t-IsoP = 15-F2t-Isoprostane; TBARS = Thiobarbituric Reactive Substances; TAP = Total Antioxidant Power; IL = Interleukin.*

Subjects attending > 60% of the training lessons (n = 18)						
	T0	**T1**	**T2**	**T0 *vs* T1**	**T1 *vs* T2**	**T0 *vs* T2**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p – value*	*p – value*	*p – value*
Quality of Life (QOL)						
WHOQOL-brief – physical domain	16.00 (3.00)	16.00 (3.14)	16.57 (3.86)	0.806	0.244	0.608
WHOQOL-brief – psychological domain	14.34 (3.33)	14.00 (3.00)	14.67 (2.50)	0.166	0.209	**0.013**
WHOQOL-brief – social relationship domain	14.67 (4.00)	14.67 (4.00)	14.67 (3.67)	0.403	0.121	0.812
WHOQOL-brief – environmental domain	15.00 (2.38)	15.50 (2.75)	15.00 (1.88)	0.278	0.843	0.293
Healthy Days – physical aspect	29.00 (1.25)	29.00 (2.50)	29.50 (2.00)	0.916	0.765	0.968
Healthy Days – psychological aspect	27.00 (4.00)	28.00 (4.50)	29.50 (2.75)	0.777	**0.007**	**0.009**
Healthy Days – usual activities	30.00 (0.00)	30.00 (1.50)	30.00 (0.75)	0.458	0.236	0.655
Healthy Days – total	26.50 (4.75)	26.00 (6.00)	28.50 (3.50)	1.000	**0.019**	0.058
BMI	25.55 (6.09)	25.00 (5.61)	25.28 (5.19)	**0.003**	0.301	0.058
Biomarkers						
15-F_{2t}-IsoP [ng/mg crea]	3.54 (1.90)	2.51 (0.89)	2.53 (1.50)	**0.002**	0.193	0.010
TBARS [µmol MDA/mmol crea]	0.08 (0.08)	0.05 (0.06)	0.05 (0.11)	0.185	0.136	0.959
TAP [mmol Trolox eq./mmol crea]	0.45 (0.15)	0.35 (0.17)	0.46 (0.15)	**0.019**	**0.044**	0.394
IL-6 [pg/mg crea]	1.58 (1.42)	1.33 (1.16)	1.12 (0.93)	0.122	0.795	0.149
IL-10 [pg/mg crea]	1.33 (3.71)	0.98 (1.14)	0.94 (2.15)	0.149	0.501	0.185

Table 6: Comparisons among the three sampling points concerning QoL, BMI and biomarkers in the high attendance group. *IQR = Inter-Quartile Range; 15-F-2t-IsoP = 15-F2t-Isoprostane; TBARS = Thiobarbituric Reactive Substances; TAP = Total Antioxidant Power; IL = Interleukin.*

Subjects attending < 60% of the training lessons (n = 8)						
	T0	**T1**	**T2**	**T0 *vs* T1**	**T1 *vs* T2**	**T0 *vs* T2**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p – value*	*p – value*	*p – value*
Quality of Life (QOL)						
WHOQOL-brief – physical domain	16.86 (4.28)	16.00 (4.40)	16.57 (4.57)	0.345	**0.042**	0.892
WHOQOL-brief – psychological domain	13.34 (4.17)	14.67 (4.50)	12.67 (4.67)	**0.011**	**0.041**	0.068
WHOQOL-brief – social relationship domain	14.00 (2.67)	14.67 (2.00)	14.67 (4.00)	0.071	1.00	0.194
WHOQOL-brief – environmental domain	14.75 (2.13)	14.75 (4.00)	14.00 (3.50)	0.325	0.786	0.931
Healthy Days – physical aspect	29.00 (3.00)	30.00 (4.50)	30.00 (2.00)	1.000	0.285	0.102
Healthy Days – psychological aspect	29.00 (5.00)	28.50 (4.75)	29.00 (7.00)	1.000	0.705	1.000
Healthy Days – usual activities	30.00 (1.00)	30.00 (3.75)	30.00 (2.00)	0.461	0.180	1.000
Healthy Days – total	27.50 (8.75)	25.50 (7.75)	28.00 (10.00)	0.916	0.244	0.416
BMI	25.22 (8.82)	24.94 (8.54)	26.41 (6.88)	0.401	**0.345**	0.753
Biomarker						
15-F_{2t}-IsoP [ng/mg crea]	4.25 (2.25)	2.99 (1.53)	3.39 (1.48)	**0.043**	0.116	0.345
TBARS [µmol MDA/mmol crea]	0.07 (0.03)	0.08 (0.24)	0.08 (0.10)	0.889	0.752	0.917
TAP [mmol Trolox eq./mmol crea]	0.56 (0.30)	0.42 (0.20)	0.53 (0.23)	0.093	0.249	0.753
IL-6 [pg/mg crea]	1.34 (1.45)	0.86 (0.90)	1.00 (1.60)	**0.025**	0.600	**0.046**
IL-10 [pg/mg crea]	2.90 (4.95)	0.62 (0.74)	0.78 (1.78)	0.063	0.345	0.249

Table 7: Comparisons among the three sampling points concerning QoL, BMI and biomarkers in subjects attending less than the the 60% of the training lessons

Figures 15-18 display the variation in QoL and biomarkers at the three sampling points in subjects attending more than 60 % of the training, subjects attending less than 60 % of the training and in the whole participants group.

From a biological point of view, in the whole epidemiological sample the comparison between T1 and T0-resulted in a significant reduction in BMI and 15-F2t-Isop, TAP, IL-6, and IL-10. After the summer period (T2 *vs* T1), we could observe only a significant rise in TAP, whose median concentration 3 months after the end of the intervention was similar to the one observed in T0. The comparison between the values measured at the end and at the beginning of the study (T2 *vs* T0) revealed the persistence of lower values in 15-F2t-Isop and IL-10. No significant differences were highlighted in terms of QoL comparing T1 and T0, with the only exception of a reduction in the WHOQOL-bref psychological domain, although we observed an improvement concerning the lowest values recorded in T0 (Figure 19). After the summer period (T2 vs T1) we observed a significant increase in the physical (WHOQOL-Bref) and psychological (Healthy Days) domains and in the total number of Healthy Days. The comparison between the values reported at the end and at the beginning of the study (T2 *vs* T0) revealed a significant increase in the psychological domain scores (WHOQOL-Bref and Healthy Days) and in the total number of Healthy Days.

Other significant modification observed were a decrease in the red meat consumption over time and a reduction in the concern for the pandemic between T1 and T0.

The comparisons among the three sampling points according to the different attendance to the training lessons provided some interesting insights. From a biological point of view, the comparison between T0 and T1 revealed that the significant decrease in 15-F2t-Isop could be measured in both subgroups, while the significant decrease in BMI and TAP were measured only in those attending more than 60% of the training. On the contrary, the significant decrease in IL-6 was observed only in the poor attendance subgroup. After the splitting, the difference in IL-10 median values pre- and post-intervention were no longer significant in any subgroup. The comparison between T2 and T1 highlighted that the significant reduction in TAP was significant only in the high attendance subgroup, while the poor attendance subgroup reported a rise in the BMI score. The comparison between T2 and T0 revealed that the significant reduction in 15-F2t-Isop observed in the whole group was confirmed only in subjects performing more than 60% of the lessons. In subjects attending less than the 60% of the training we observed a significant decrease in IL-6, while the significant difference in IL-10 measured in the whole group was no longer significant in any subgroup.

Concerning the QoL, in the comparison between the T0 and T1, the significant reduction in the WHOQOL-bref psychological domain was not confirmed in the high attendance subgroup, while, on the contrary, a significant increase was observed in the poor attendance group. The comparison between T1 and T2 confirmed the significant increase in psychological health (Healthy Days) and in the total number of Healthy Days in subjects attending the workout. In the poor attendance subgroup, we could observe an increase in the physical and in the psychological domain (WHOQOL-bref). The comparison between T0 and T2 confirmed the significant increase in the psychological domain (WHOQOL-bref and Healthy Days) in the high attendance group.

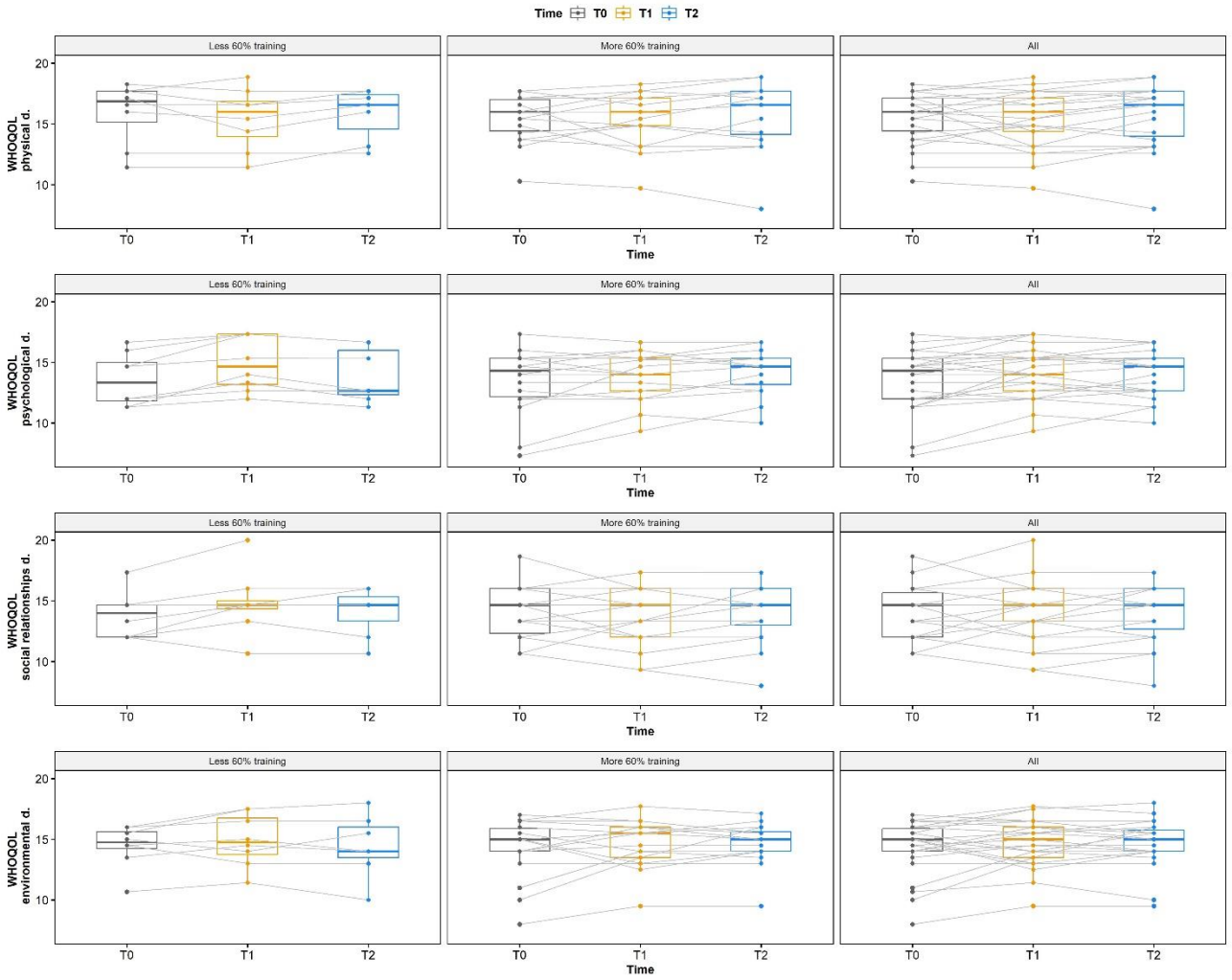


Figure 15: QoL (WHOQOL-bref) among participants at the three sampling points, T0, T1, and T2. Each boxplot shows the median, the 1st and the 3rd quartiles. The first two faces include subjects according to different attendance to the training lessons (more and less than 60%), while in the last includes the whole participants' group. Jitters represents the data of each individual, grey lines join data of the same subjects obtained at T0, T1, and T2.

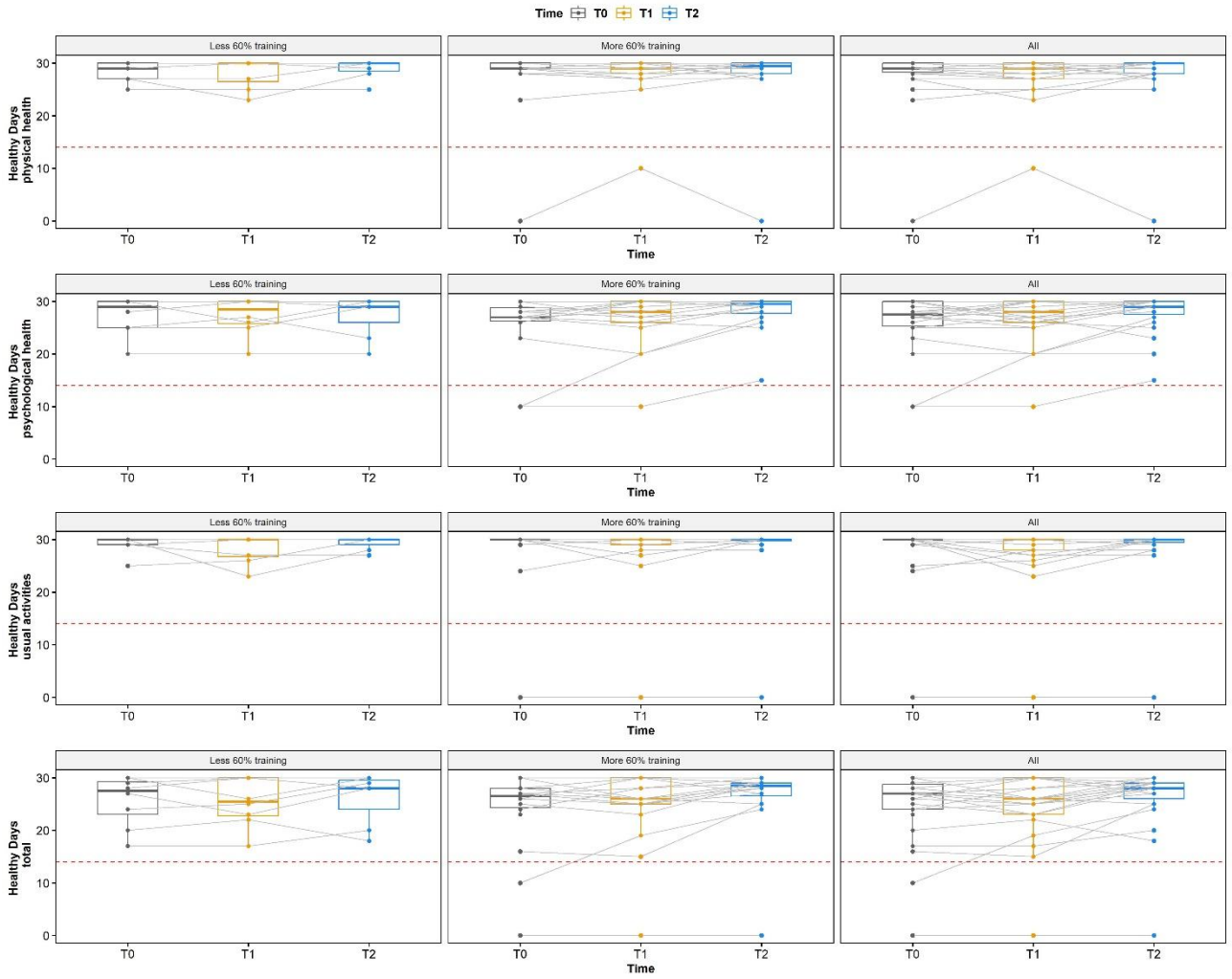


Figure 16: QoL (Healthy Days) among participants at the three sampling points, T0, T1, and T2. Each boxplot shows the median, the 1st and the 3rd quartiles. The first two faces include subjects according to different attendance to the training lessons (more and less than 60%), while in the last includes the whole participants' group. Jitters represents the data of each individual, grey lines join data of the same subjects obtained at T0, T1, and T2. The red dashed lines represent the cut-off of 14 days.

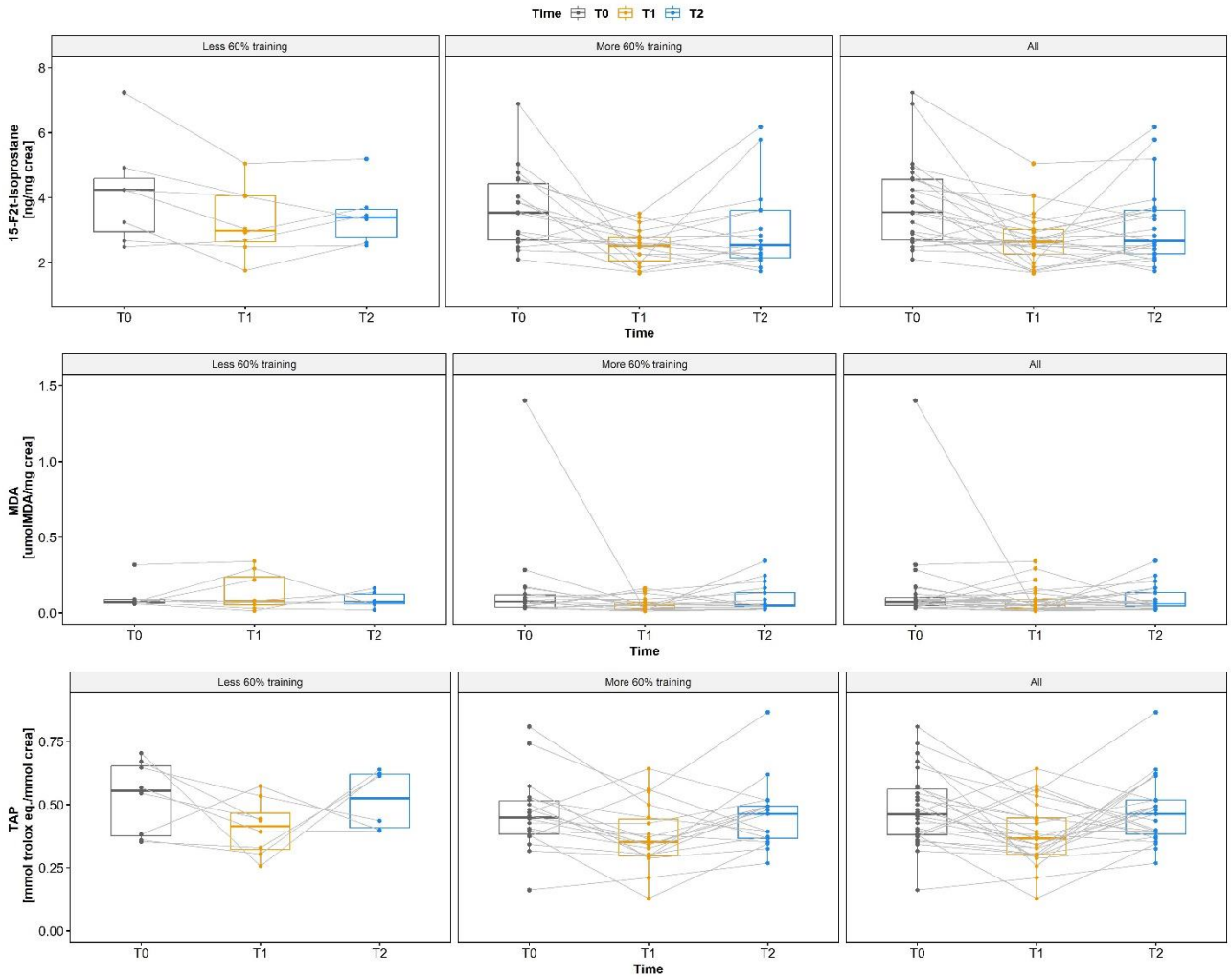


Figure 17: Urinary concentration of oxidative stress biomarkers at the three sampling points, T0, T1, and T2. Each boxplot shows the median, the 1st and the 3rd quartiles. The first two faces include subjects according to different attendance to the training lessons (more and less than 60%), while in the last includes the whole participants' group. Jitters represents the data of each individual, grey lines join data of the same subjects obtained at T0, T1, and T2.

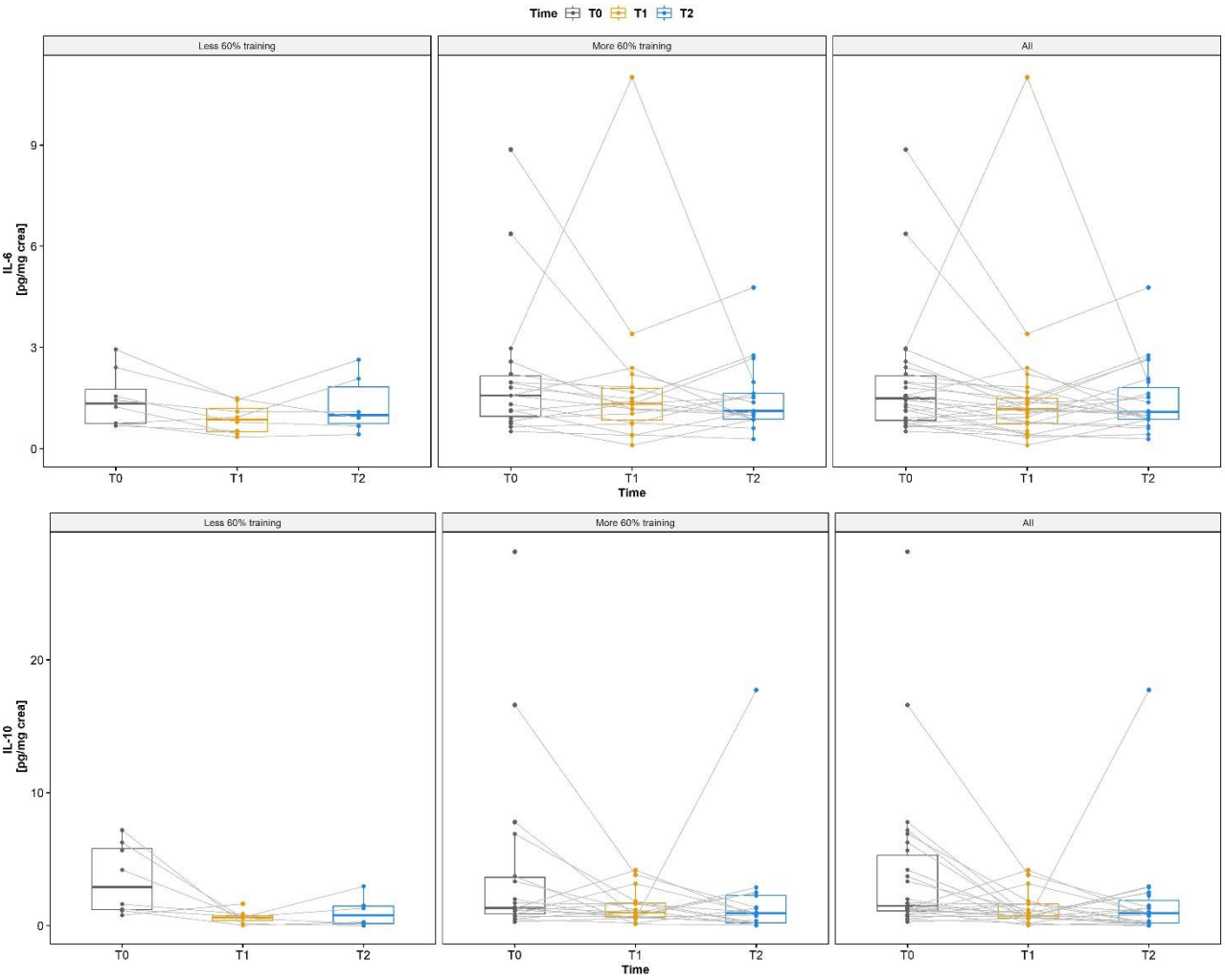


Figure 18: Urinary concentration of inflammatory biomarkers at the three sampling points, T0, T1, and T2. Each boxplot shows the median, the 1st and the 3rd quartiles. The first two faces include subjects according to different attendance to the training lessons (more and less than 60%), while in the last includes the whole participants' group. Jitters represents the data of each individual, grey lines join data of the same subjects obtained at T0, T1, and T2.

3.2.1.4. Discussion

The purpose of our study to analyse the potential benefit of a WEB-based workout program in office workers, aiming to suggest, whether possible, key elements to be implemented in sustainable strategies to promote workers' well-being.

Indeed, a working environment where workers and managers are collaborating to improve the health, safety, and well-being of the workforce, sustaining thus also business productivity, can be defined as a healthy workplace (Burton 2010). Sustainable employment and appropriate working conditions are critical to ensure workers to remain at work despite ageing, increasing their workability (Neupane et al. 2022).

Office workers, are at high risk of developing several chronic diseases (*e.g.* musculoskeletal disorders, obesity, cardio-metabolic diseases, and metabolic syndrome), associated with general reduction of workers' QoL and to both lost productivity and increasing health care needs (İkiz and Ergin 2023; Nguyen, Nguyen, and Kim 2021; Holzgreve et al. 2021; Chang et al. 2020). In these settings PA can be implemented in cost-effective interventions for the management and the

prevention of many work-related chronic diseases (Nguyen, Nguyen, and Kim 2021; Durstine et al. 2013).

During pandemic, the regular practice of PA turned out to be even more valuable. Indeed, people who exercised daily during lockdowns reported fewer somatisation symptoms, lower stress levels, more normal sleep, and a general reduction in depression and anxiety symptoms than those who did not exercise (Violant-Holz et al. 2020).

Moreover, WEB-based tools had been widely and successfully employed to target modifiable behavioural health risk factors (*e.g.,* sedentary lifestyle, low PA, and the consumption of nutrient-poor energy-dense foods) to prevent obesity, and other non-communicable diseases (Wolf et al. 2021; Hutchesson et al. 2021). Dietary risk factors and physical inactivity were estimated in 2010 to account for 10% of all deaths and disability-adjusted life years (DALYs) globally, while a high BMI for 3.8% of DALYs, revealing the need of effective intervention strategies applicable at large-scale (Hutchesson et al. 2021; Lim et al. 2012). The WEB-based training allows to overcome a number of limitations (*e.g.* those related to the pandemic containment), and the opportunity to take part in virtual lessons with friends, colleagues, or a virtual community might be a key factor in preventing the isolation and the lack of social support (Wolf et al. 2021).

In the whole epidemiological sample, we did not observe any significant variation in the QoL perception after the intervention period, except for a reduction in the median scores of the WHOQOL-bref psychological domain not confirmed in the high attendance group. This fluctuation could be likely related to the small number of subjects enrolled, emphasising the lowering of the scores in some subjects. The significant improvement observed, instead, after the summer period, could be likely related to a more relaxing and maybe healthier lifestyle typical of the holiday period.

PA can exert its beneficial role influencing various bio-molecular pathways, including oxidative and inflammatory status that are interdependent pathophysiological processes associated with several chronic diseases, including diabetes, hypertension and cardiovascular diseases, neurodegenerative diseases, cancer, and ageing (Biswas 2016). Several studies to date focus their attention on the role of PA in shaping oxidative and inflammatory status, especially the concentration of urinary isoprostanes (Squillacioti et al. 2021; Schuch et al. 2016).

We analysed thus urinary concentration of multiple biomarkers as a proxy of the role of PA in modulating these molecular mechanisms. As expected, the bio-molecular profile revealed a clearer effect of the PA administration. Indeed, concerning the oxidative status, in T1 we observed a significant reduction in both the 15-F2t-IsoP and TAP concentration. Considering the different training attendance, while the decrease in 15-F2t-IsoP was detected in both subgroups, the decrease in TAP was observed only in the high attendance subgroup. Three months after the end of the intervention we assisted to a significant increase in TAP, again confirmed only in subjects having performed more than 60% of the training lessons. Our results are in line with our previous work (Squillacioti et al. 2021), reporting that, while vigorous PA is related to an increase in oxidative stress, the regular practise of moderate PA is able to reduce the oxidative burden.

The similar trend between the concentration of 15-F2t-IsoP and the antioxidants which can be observed in the high attendance subgroup was unexpected, even if reported in literature (González et al. 2020). Even our data do not allow us to support this hypothesis and further studies properly characterising the antioxidant profile would be mandatory, we supposed a possible role of adaptive molecular pathways evolved such that common processes responsible for an increase in pro-oxidants (*e.g.*, PA and critical illness) that can lead to the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor playing a key role in enhancing the antioxidant production to maintain the redox homeostasis (Zgorzynska, Dziedzic, and Walczewska 2021; González et al. 2020). Nrf2 can also induce its own expression, resulting in a positive feedback activation of its transcriptional network (Chen and Maltagliati 2017).

We might thus hypothesise that the prolonged exercise is able to trigger a general rebalancing of the oxidative status, with a reduction in the oxidative burden confirmed by the reduction in the antioxidant concentration. This relation seems to be supported by the reverse in the biomarkers' concentration after the end of the intervention. The significant increase in TAP may be interpreted as an attempt to re-establish a redox balance due to a possible increase in pro-oxidants. The data reported in T2 could have been affected in many ways by the changes in lifestyle, either positive or negative, due to the summer life.

Concerning the inflammatory status, we focused our attention on IL-6, a pro-/anti-inflammatory cytokine involved in the response to several stimuli, including exercise (Zhang and An 2007; Fischer 2006), and IL-10, an anti-inflammatory immune-suppressive cytokine (Ogawa, Duru, and Ameredes 2008) which could be modulated by PA (Rossi et al. 2022; Najafi et al. 2022). At T1, in the whole sample, we observed a significant reduction in both biomarkers, even if these differences disappeared in the high attendance subgroup.

The main strength of the study consists in the simultaneous investigation of both the QoL and the bio-molecular profile, in relation to an intervention as the physical activity administration that could have beneficial effects on both the perspectives. This intervention seemed to be able to provide beneficial effects to the participants, as evidenced by the improvement in the oxidative and inflammatory status. Secondly, the adoption of a WEB-based intervention was cost-effective and easy to implement for a huge number of workers, in a wide spectrum of working settings, even when they are working from home. This last point is even more valuable to improve also the social support among workers, especially in the perspective of a foreseeable change in the work organization after the pandemic. Thirdly, the PA sessions were supervised by a skilled trainer, strengthening the importance of the presence of professionals with an extensive knowledge in ergonomics and biomechanics in working environment to prevent and treat musculoskeletal injuries (Moreira et al. 2022). The main weaknesses can be identified, instead, in the small number of volunteers taking part in the project and in the absence of multiple settings investigated, preventing to carry out a refined data analysis able to highlight the eventual role of confounders such as the concern of the pandemic and lifestyle factors in modulating the studied outcomes. Secondly, the antioxidant and inflammatory profiles need to be more deeply investigated, characterising the biological response in terms of a more exhaustive list of biomarkers (*e.g.*, superoxide dismutase, catalase, glutathione peroxidase, and IL-8), also to investigate the potential role of the Nrf2 pathway, as suggested. Thirdly, the duration of the intervention was very limited, possibly preventing the observation of significant effects on QoL. These features highlight the need to consider cautiously the results observed. If these results were confirmed in studies involving larger samples, it would be confirmed the beneficial effects of PA-based health promotion programs, even with the implementation of mild interventions, suitable to the vast majority of subjects, and as inclusive as possible, even in populations heterogeneous in terms of socio-demographic variables and health status.

Further studies would be desirable to create standard protocols which could be employed in the different working environments as a routine part of health promotion programs, with a particular focus on the specific needs of an ageing workforce.

3.2.2. Study Line 2: Health Promotion in Working Environment

3.2.2.1. Material and methods

3.2.2.1.1. Aim

The aim of the present Study Line was the assessment of the QoL in an Italian population of workers after the toughest phases of the COVID-19 pandemic, evaluating the possible contribution of lifestyle factors and working conditions in modulating this perception.

3.2.2.1.2. Study Design

A questionnaire was administered to a sample of Italian workers. Since no information allowing the identification of respondents was collected, the data obtained were completely anonymous. The access to the questionnaire was considered as an agreement to participate to the study. The link to the questionnaire was delivered to all the workers employed in a Italian plant by the HR manager the 28th June 2021 and was made available for the next three weeks.

3.2.2.1.3. Epidemiological Sample and Recruitment

All workers employed in the Italian plants (located in the Veneto and Emilia-Romagna regions, in the North of Italy) of an Italian company operating in the field of GreenBuilding solutions (n = 660) had been invited to fill out the questionnaire. To maximise the workers' compliance, the Company combined the questionnaire filling to the possibility to participate to a raffle.

3.2.2.1.4. Questionnaire

Each subject filled out a comprehensive questionnaire covering a broad range of factors, including demographic variables (sex, age), concern for the pandemic, lifestyle (smoking status and physical activity intensity level), and habits (smoking status, PA and food frequency (number of times/weeks each subject eats fruits and vegetables, red meat, and fish), QoL. The questionnaire was self-administered by the Lime Survey platform (2012, Hamburg, Germany) and the link was made available on the sampling day.

3.2.2.1.4.1. WHOQOL-bref

(as described for *Study Line 1*)

3.2.2.1.4.2. Healthy Days

(as described for *Study Line 1*)

3.2.2.1.4.3. International Physical Activity Questionnaire (IPAQ)

(as described for *Study Line 1*)

3.2.2.1.4.4. Work-related factors

3.2.2.1.4.4.1. Burnout

The level of exhaustion was assessed by the specific eight items from the Oldemburg Burnout Inventory (OLBI). The items were measured with a 5-point Lickert scale, from 1 (“Strongly disagree”) to 5 (“Strongly agree”) (Demerouti, Mostert, and Bakker 2010). The Cronbach’s α was > 0.7.

3.2.2.1.4.4.2. Job Insecurity

The Job Insecurity was assessed through the four items of the De Witte scale. The items were measured with a 5-point Lickert scale, from 1 (“Strongly disagree”) to 5 (“Strongly agree”) (de Witte 2000). The Cronbach’s α was > 0.7.

3.2.2.1.4.4.3. Job Autonomy

The Job Autonomy was assessed by the six items of the scale by Karasek and Theorell. The items were measured with a 4-point Lickert scale, from 1 (“None”) to 5 (“A lot”) (Zito et al. 2018). The Cronbach’s α was > 0.7.

3.2.2.1.4.4.4. Workload

Workload was measured by the 4-item scale of Bakker and colleagues. The items were measured with a 5-point Lickert scale, from 1 (“Never”) to 5 (“Always”) (Bakker, Demerouti, and Verbeke 2004). The Cronbach’s α was > 0.7.

3.2.2.1.4.5. Number of diseases

The number of diseases was assessed by means of the list of diseases from the Work Ability Index (Tuomi et al. 1998).

3.2.2.1.5. Statistical analysis

Statistical analyses were performed by SPSS Statistics 28 (IBM SPSS Statistics, New York, NY, USA). Graphs were created by R Studio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA).
Categorical variables have been reported as frequency (n) and percent (%) and compared by the χ squarewd test, while continuous variables have been reported as median and interquartile range (IQR). Wilcoxon’s Signed-Rank Test or Kruskal-Wallis test were employed to compare ordinal data and continuous variables. The Cronbach α was calculated for WHOQOL-bref questionanires and for work-related factors scales (Workload, Exhaustion, Job Insecurity and Job Autonomy).
Specifically, to discriminate different levels of QoL, we performed a cluster analysis (k-mean method) based on the four domains of the QoL identificated by the WHOQOL-bref questionnaire. We then compared the clusters in terms of personal characteristics (age, BMI, and number of diseases), QoL (WHOQOL-bref and HD), and work-related factors (Workload, Emotional Exhaustion, Job Insecurity, and Job Autonomy). The significance level of the tests was 0.05. The mediation analysis wa performed by a series of regression models, according to the Hayes’ method. We assumed that Emotional Exhaustion could be a possible mediator of the impact on QoL of personal and work-related characteristics. Specifically, in each model we included: (i) two factors related to the lifestyle and health conditions, which could have a positive (physical activity level) and a negative (n. of diseases) impact on exhaustion, respectively; (ii) three work related factors with a known relationship with exhaustion and burnout, also in this case with a potential positive (Job Autonomy)

and negative (Workload and Job Insecurity) impact on Emotional Exhaustion; (iii), confounders, which may have play a role, even marginal, on shaping this relationship (sex, classification (*i.e.* being white- or blue-collars), age, smoking habit). The Physical Activity level was considered as a categorical variable, grouping those actively performing PA, either at medium or high intensity, vs those with only low intensity.

3.2.2.2. Results

337 subjects took voluntarily part our survey as a consecutive sample. The response rate of the survey was 51.1%, only 76% providing a complete report. The age range of respondents were 21-63 years (min-max), 66% males, 79% white-collars.

The k-means cluster analyses performed on the four QoL domains of the WHOQOL-bref allowed us to identify three cluster of subjects with different QoL levels: Low, Medium, and High (**Table 8** and **Figure 19**).

WHOQOL-bref domains	Low QOL (*n* = 94)	Medium QOL (*n* = 155)	High QOL (*n* = 83)
Physical	12.91 ± 1.79	15,38 ± 1.25	17.23 ± 1.15
Psychological	12.20 ± 1.32	14.60 ± 1.16	16,52 ± 1.11
Social relationship	12.93 ± 2.24	15.13 ± 1.55	16.82 ± 1.48
Environmental	11.98 ± 1.76	14.08 ± 1.22	15.78 ± 1.33

Table 8: Means ± standard deviations of the centre values of the three clusters.

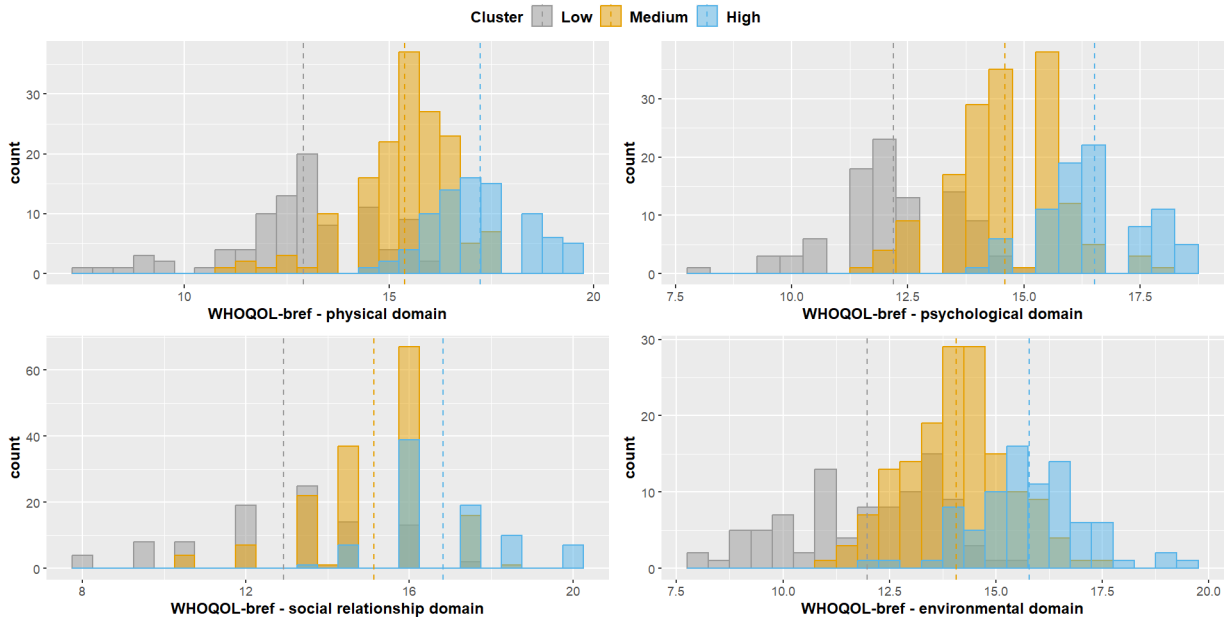


Figure 19: Cluster analysis

The characteristics of the epidemiological sample are reported in **Table 9**, according to the different cluster in which each subject was classified after the cluster analysis. The comparisons among the frequences and scores obtained, revealed significant differences among the cluster for the most of the variables investigated. **Figures 20-22** dispalyed the differences in personal characteristics (age, BMI, and n. of diseases), QoL (WHOQOL-bref and Healthy Days) and work-related factors (Workload, Emotional Exhaustion, Job Autonomy, Job Insecurity).

	QoL cluster			
	Low (n = 94)	***Medium (n = 155)***	***High (n = 83)***	***p-value***
	n (%)	*n (%)*	*n (%)*	
Sex				0.063
F	38 (40.90%)	49 (32.00%)	19 (24.10%)	
M	55 (59.10%)	104 (68.00%)	60 (75.90%)	
Education				0.074
Middle school license	13 (13.80%)	7 (4.50%)	13 (15.70%)	
High-school license	44 (46.80%)	79 (51.00%)	32 (38.60%)	
Degree	29 (30.90%)	51 (32.90%)	30 (36.10%)	
Post-graduate specialisation	8 (8.50%)	18 (11.60%)	8 (9.60%)	
Concerning for the pandemic				**0.08**
Not at all/Low	21 (22.90%)	45 (29.00%)	28 (33.70%)	
Fairly	43 (45.70%)	69 (44.50%)	43 (51.80%)	
High/Very High	30 (31.90%)	41 (26.50%)	12 (14.50%)	
Smoking habit				0.644
Currently smokers	20 (21.30%)	28 (18.10%)	19 (22.90%)	
Not current smokers	74 (78.70%)	127 (81.90%)	64 (77.10%)	
Sleep hours				**0.06**
< 6 h / die	23 (24.50%)	26 (16.80%)	9 (11.00%)	
≥ 6 h / die	71 (75.50%)	129 (83.20%)	73 (89.00%)	
Physical activity level				0.437
Low	31 (41.90%)	37 (31.10%)	22 (29.30%)	
Medium	20 (27.00%)	43 (36.10%)	25 (33.30%)	
High	23 (31.10%)	39 (32.80%)	28 (37.30%)	
Classification				0.243
Blue-collars	22 (23.70%)	28 (18.10%)	19 (22.90%)	
White-collars – employees	62 (66.70%)	103 (66.50%)	47 (56.60%)	
White-collars – managers	9 (9.70%)	24 (15.50%)	17 (20.50%)	
Working years				0.487
0 – 5 yrs.	28 (29.80%)	57 (36.80%)	35 (42.20%)	
5-15 yrs.	33 (35.10%)	50 (32.30%)	27 (32.50%)	
>15 yrs.	33 (35.10%)	48 (31.00%)	21 (25.30%)	
Working activity in line with the education				**0.004**
No	23 (24.50%)	20 (12.90%)	6 (7.20%)	
Yes	71 (75.50%)	135 (87.10%)	77 (72.80%)	
Changes in the working activity due to the pandemic				**0.045**
No	73 (77.70%)	114 (73.50%)	51 (61.40%)	
Yes	21 (22.30%)	41 (26.50%)	32 (38.60%)	

Table 9a: Comparisons among the different QoL clusters identified.

	QoL cluster			
	Low (n = 94)	***Medium (n = 155)***	***High (n = 83)***	***p-value***
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	
Age (yrs.)	43 (15)	40 (16)	38 (17)	**0.033**
BMI	24.06 (3.58)	24.07 (5.02)	23.91 (4.06)	0.757
N. of diseases	3 (4)	1 (2)	1 (2)	**< 0.001**
WHOQOL-bref – Physical domain	13.14 (2.29)	15.43 (1.14)	17.14 (1.71)	**< 0.001**
WHOQOL-bref – Psichological domain	12.00 (2.00)	14.67 (1.33)	16.67 (1.33)	**< 0.001**
WHOQOL-bref – Social relationship domain	13.33 (2.67)	16.00 (1.33)	16.00 (1.33)	**< 0.001**
WHOQOL-bref – Environmental domain	12.25 (2.5)	14.00 (1.50)	15.50 (1.50)	**< 0.001**
HD – Physical health	28 (6.5)	28 (3)	30 (2)	**< 0.001**
HD – Psychological health	25 (13)	29 (3.25)	30 (2)	**< 0.001**
HD – Capability to perform usual activities	30 (3)	30 (1)	30 (0)	**< 0.001**
HD – Total	22 (18)	27 (5)	28 (3)	**< 0.001**
Job insecurity	2 (1.25)	1.75 (0.85)	1.25 (0.8)	**< 0.001**
OLBI – Exhaustion	20 (6)	16 (5)	14 (5)	**< 0.001**
Workload	3.75 (1.25)	3 (1)	3 (1.25)	**< 0.001**
Job autonomy	3.67 (1.33)	3.67 (1)	4 (1)	**0,002**

Table 9b: Comparisons among the different QoL clusters identified.

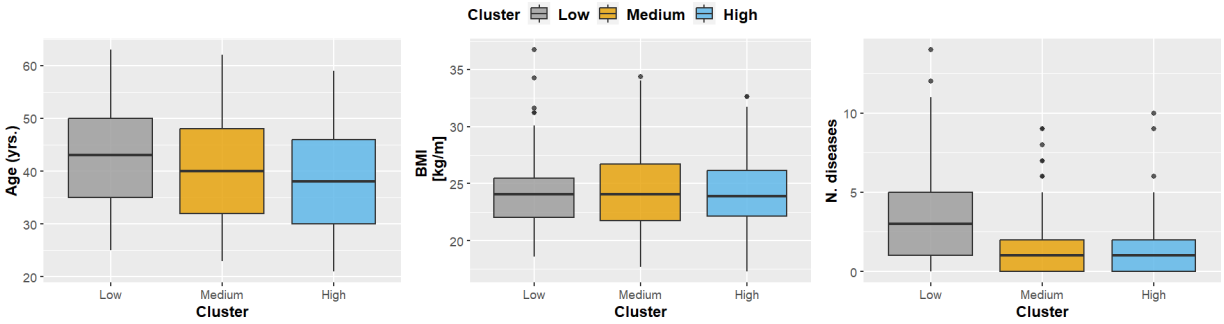


Figure 20: Personal characteristics in the three clusters.

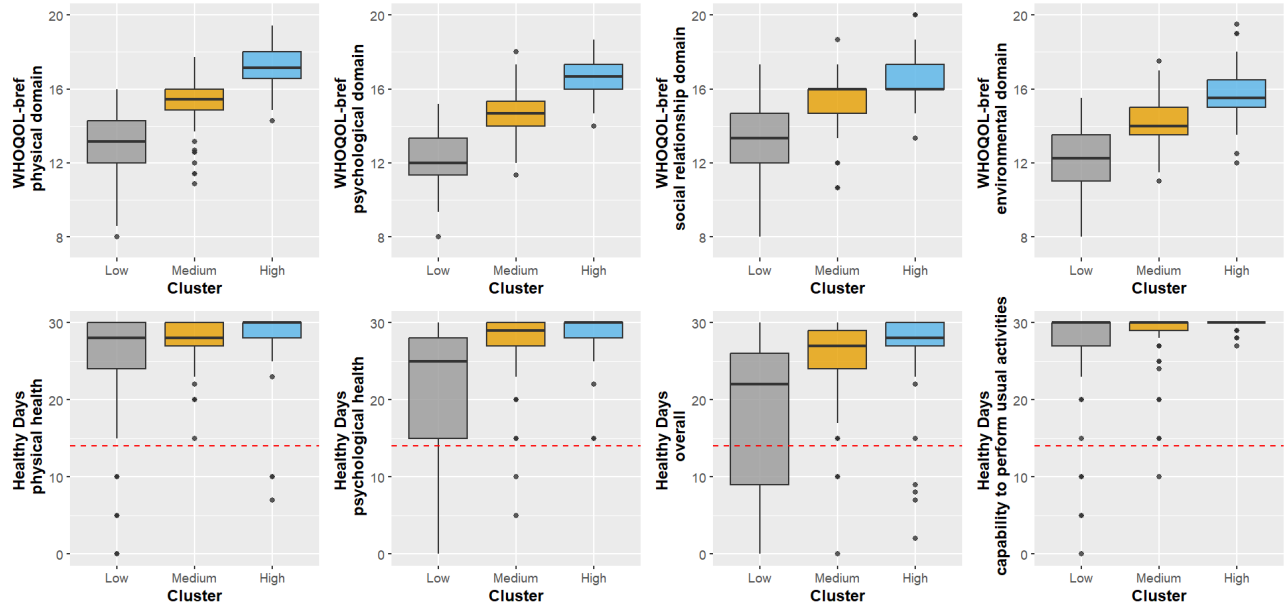


Figure 21: QoL in the three clusters identified.

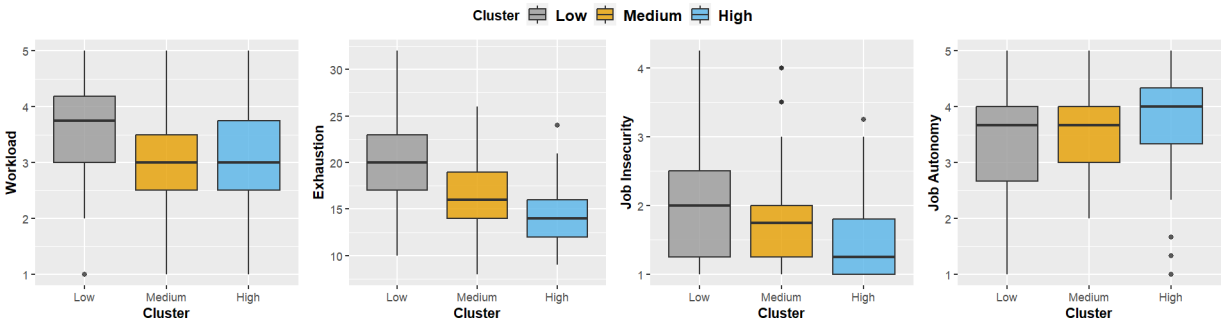


Figure 22: Characteristics of the working activity in the three clusters identified.

The post-hoc analysis related to the Kruskal-Wallis test to compare the significant differences among the three clusters, revealed that subjects in the Low-QoL cluster were significantly older than the ones in the High-QoL ($p = 0.028$) and that suffered for a significantly higher number of pathologies than both the ones in the Medium- and High-QoL ($p < 0.001$ and $p = 0.001$, respectively).

Concerning the WHOQOL-bref scores, the analysis revealed a significant difference in all the comparisons among the three groups (all $p < 0.001$). As well, the comparisons of the number of healthy days revealed a significant difference among the three groups, with the only exception of the comparison between Medium and High clusters for the Psychological health (Physical health: Low vs Medium $p = 0.03$, Low vs High $p < 0.001$, Medium vs High $p = 0.011$; Psychological health: Low vs Medium $p < 0.001$, Low vs High $p < 0.001$, Medium vs High p = ns; capability to perform usual activities: Low vs Medium $p = 0.001$, Low vs High $p < 0.001$, Medium vs High $p = 0.019$). Concerning the work-related factors, subjects in the High-QoL cluster had a significantly lower perception of job insecurity, exhaustion, and workload than subjects in both the Medium- and Low-QoL groups (all ps < 0.001 except for High vs Medium for exhaustion $p = 0.001$). Subjects in the Low-QoL group revealed significantly lower exhaustion scores than those in the Medium-QoL group ($p < 0.001$). As expected, the perception of Job autonomy was significantly higher in the High-QoL cluster than in the Low- one, the other comparison did not reveal any significance.

Mediation analysis

A mediation analysis was performed to assess the eventual role of some of the variables included on the different domains of QoL obtained by the administration of the WHOQOL-bref, assuming that this effect could be mediated by the Exhaustion. Specifically we enter in each model: (i) two factors related to the lifestyle and health conditions, which could have a positive (physical activity level) and a negative (n. of diseases) impact on exhaustion, respectively; (ii) three work related factors with a known relationship with exhaustion and burnout, also in this case with a potential positive (Job Autonomy) and negative (Workload and Job Insecurity) impact on Exhaustion; (iii), confounders, which may have play a role, even marginal, on shaping this relationship (sex, classification, age, smoking habit). A scheme of the mediation model considered is reported in **Figure 23**.

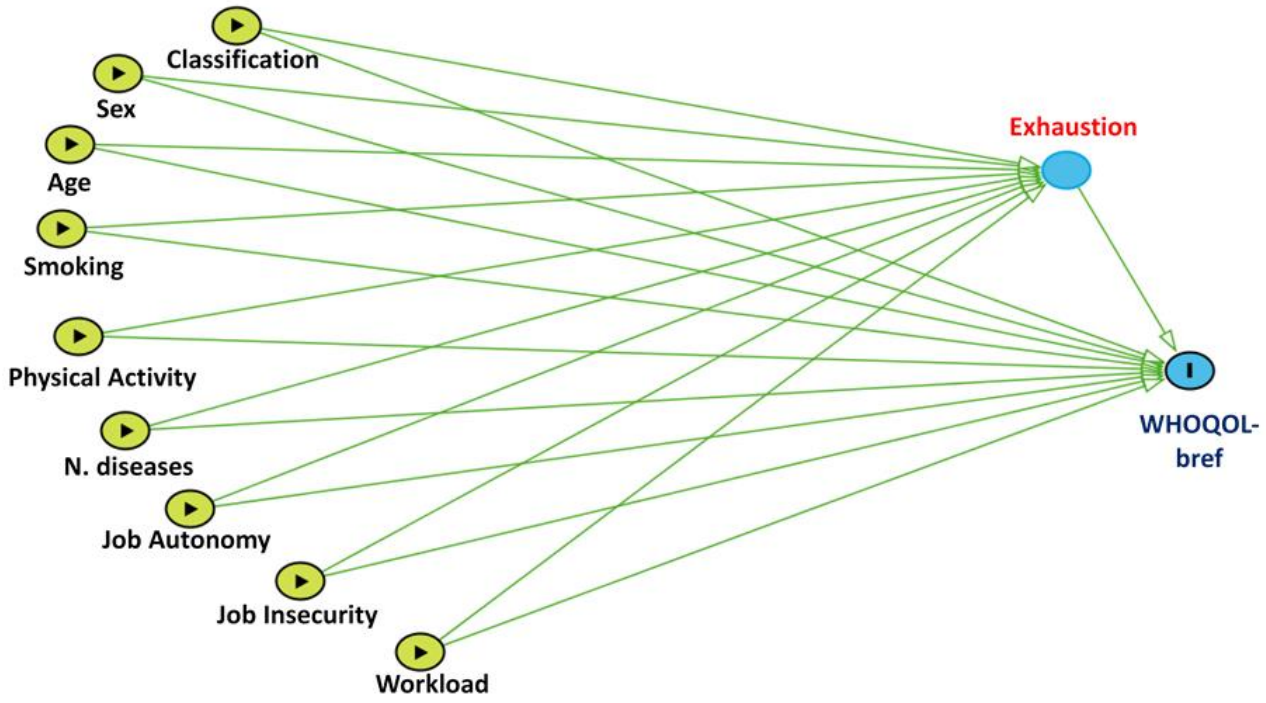


Figure 23: Scheme of the variables included in the mediation analyses.

The mediation analysis revealed some interesting relationships. The results of the mediation analyses concerning each QoL domain identified by the WHO are reported in **Tables 10 - 13**.

In model 1 we investigated the effects of the selected variables on the physical domain (**Table 10**). Workload (β = 0.42, 95% C.I. (0.331, 0.509), p < 0.001), Job Autonomy (β = −0.34, 95% C.I. (−0.435, −0.239), p < 0.001) and medium-to-high PA level (β = −0.11, 95% C.I. (−0.213, −0.012), p = 0.029) significantly affected Emotional Exhaustion (EE), which had a negative relationship with QoL (β = −0.48, 95% C.I. (−0.580, −0.380), p < 0.001). At the same time, we observed that PA still maintained a positive impact on QoL (β = 0.11, 95% C.I. (0.023, 0.198), p = 0.014), revealing the multiple role of PA in improving QoL, at least concerning the physical domain. We observed a full mediation for WL. EE did not mediate the negative effect of diseases (β = −0.32, 95% C.I. (−0.400, −0.231), p = 0.000), age (β = −0.21, 95% C.I. (−0.293, −0.118), p = 0.000), and JI (β = −0.14, 95% C.I. (−0.232, −0.054), p = 0.002) on QoL. The role of JA is unexpected, maintaining also a negative effect on physical QoL (β = −0.15, 95% C.I. (−0.246, −0.054), p = 0.003).

n = 255	β	p-value	z-value	95% C.I.		R^2	R^2 - adj
Exhaustion						0.336	0.312
Workload	0,42	**0,000**	9,23	0.331	0.509		
Job Insecurity	0,10	0,056	1,93	-0.002	0.204		
N. of diseases	0,10	0,057	1,91	-0.002	0.202		
Job Autonomy	-0,34	**0,000**	-6,77	-0.435	-0.239		
Physical activity level (1 = medium – high)	-0,11	**0,029**	-2,20	-0.213	-0.012		
Sex (1 = M)	0,02	0,784	0,27	-0.094	0.125		
Age (yrs.)	-0,06	0,242	-1,17	-0.165	0.041		
Smoking (1 = Yes)	0,06	0,282	10,79	-0.045	0.157		
Classification (1 = white-collars)	-0,01	0,894	-0,13	-0.113	0.099		
WHOQOL-bref physical domain						0,507	0,487
Workload	-0,06	0,198	-1,29	-0.162	0.033		
Job Insecurity	-0,14	0,002	-3,15	-0.232	-0.054		
N. of diseases	-0,32	0,000	-7,34	-0.400	-0.231		
Job Autonomy	-0,15	0,003	-3,05	-0.246	-0.054		
Physical activity level (1 = medium – high)	0,11	0,014	2,47	0.023	0.198		
Emotional Exhaustion	-0,48	0,000	-9,42	-0.580	-0.380		
Sex (1 = M)	0,07	0,147	1,45	-0.024	0.164		
Age (yrs.)	-0,21	0,000	-4,63	-0.293	-0.118		
Smoking (1 = Yes)	-0,01	0,844	-0,20	-0.096	0.079		
Classification (1 = white-collars)	-0,04	0,366	-0,91	-0.133	0.049		
Indirect effects							
Workload	-0,20	0,000	-6,44	-0.263	-0.140		
Job Insecurity	-0,05	0,058	-1,89	-0.099	0.002		
N. of diseases	-0,05	0,058	-1,90	-0.097	0.002		
Job Autonomy	0,16	0,000	5,29	0.102	0.222		
Physical activity level (1 = medium – high)	0,05	0,032	2,15	0.005	0.104		
Total Effects							
Workload	-0,27	0,000	-5,467	-0.362	-0.171		
Job Insecurity	-0,19	0,000	-3,763	-0.291	-0.092		
N. of diseases	-0,37	0,000	-7,706	-0.456	-0.271		
Job Autonomy	0,01	0,820	0,228	-0.092	0.116		
Physical activity level (1 = medium – high)	0,16	0,001	3,284	0.066	0.263		

Table 10: Model 1 – impact of the included variables on the WHOQOL-bref – physical domain

In model 2 we investigated the effects of the selected variables on the psychological domain (**Table 11**). The roles of WL (β = 0.42, 95% C.I. (0.332, 0.510), p < 0.001), JA (β = −0.34, 95% C.I. (−0.436, −0.241), p < 0.001), and medium-to-high PA level (β = −0.11, 95% C.I. (−0.212, −0.011), p = 0.030) in affecting EE remained similar to the ones previously reported. As well, EE had a negative relationship with psychological QoL (β = −0.47, 95% C.I. (−0.582, −0.352), p < 0.001). In this model we observed a full mediation for WL, JA, and PA (even though in this last case the total effects did not result significant). EE did not mediate the negative effect of JI (β = −0.15, 95% C.I. (−0.255, −0.047), p = 0.004) on this domain.

n = 256	β	p-value	z-value	95% C.I.		R^2	R^2 - adj
Exhaustion						0,337	0,313
Workload	0,42	0,000	9,28	0.332	0.510		
Job Insecurity	0,10	0,054	1,92	-0.002	0.203		
N. of diseases	0,10	0,058	1,89	-0.003	0.200		
Job Autonomy	-0,34	0,000	-6,82	-0.436	-0.241		
Physical activity level (1 = medium – high)	-0,11	0,030	-2,18	-0.212	-0.011		
Sex (1 = M)	0,01	0,809	0,24	-0.096	0.123		
Age (yrs.)	-0,06	0,234	-1,19	-0.165	0.040		
Smoking (1 = Yes)	0,06	0,285	1,07	-0.046	0.156		
Classification (1 = white-collars)	-0,01	0,898	-0,13	-0.112	0.099		
WHOQOL-bref psychological domain						0,318	0,290
Workload	-0,03	0,571	0,57	-0.149	0.082		
Job Insecurity	-0,15	0,004	-2,85	-0.255	-0.047		
N. of diseases	-0,09	0,082	-1,74	-0.196	0.012		
Job Autonomy	0,02	0,760	0,31	-0.097	0.132		
Physical activity level (1 = medium – high)	-0,05	0,315	-1,01	-0.156	0.050		
Emotional Exhaustion	-0,47	0,000	-7,94	-0.582	-0.352		
Sex (1 = M)	0,10	0,073	1,79	-0.009	0.211		
Age (yrs.)	-0,04	0,404	-0,83	-0.149	0.060		
Smoking (1 = Yes)	0,03	0,580	0,55	-0.074	0.132		
Classification (1 = white-collars)	-0,07	0,189	-1,31	-0.178	0.035		
Indirect effects							
Workload	-0,20	0,000	-5,90	-0.262	-0.131		
Job Insecurity	-0,05	0,061	-1,88	-0.096	0.002		
N. of diseases	-0,05	0,065	-1,85	-0.095	0.003		
Job Autonomy	0,16	0,000	5,08	0.097	0.219		
Physical activity level (1 = medium – high)	0,05	0,036	2,09	0.003	0.101		
Total Effects							
Workload	-0,23	0,000	-4,136	-0.339	-0.121		
Job Insecurity	-0,20	0,001	-3,46	-0.310	-0.086		
N. of diseases	-0,14	0,016	-2,399	-0.251	-0.025		
Job Autonomy	0,18	0,003	3,006	0.061	0.291		
Physical activity level (1 = medium – high)	0,00	0,988	-0,015	-0.114	0.112		

Table 11: Model 2 – impact of the included variables on the WHOQOL-bref – psychological domain

In model 3 we investigated the effects of the selected variables on the social relationship domain (**Table 12**). The roles of WL (β = 0.42, 95% C.I. (0.335, 0.513), p < 0.001), JA (β = −0.34, 95% C.I. (−0.433, −0.238), p < 0.001), and medium-to-high PA level (β = −0.11, 95% C.I. (−0.215, −0.014), p = 0.025) in affecting EE remained similar to the ones previously reported. In addition, we observe also a positive effect of the n. of diseases (β = 0.10, 95% C.I. (0.000, 0.204), p < 0.050). As well, we observed a negative relationship of the EE with QoL (β = −0.29, 95% C.I. (−0.429, −0.158), p < 0.0001). We observed a full mediation for WL, the n. of diseases, JA, and PA on QoL. In this model EE did not mediate the negative effect of age (β = −0.15, 95% C.I. (−0.265, −0.034), p < 0.011) on QoL.

n = 255	β	p-value	z-value	95% C.I.		R^2	R^2 - adj
Exhaustion						0,339	0,315
Workload	0,42	0,000	9,36	0.335	0.513		
Job Insecurity	0,10	0,058	1,89	-0.003	0.202		
N. of diseases	0,10	0,050	1,96	0.000	0.204		
Job Autonomy	-0,34	0,000	-6,74	-0.433	-0.238		
Physical activity level (1 = medium – high)	-0,11	0,025	-2,24	-0.215	-0.014		
Sex (1 = M)	0,01	0,846	0,19	-0.099	0.120		
Age (yrs.)	-0,07	0,206	-1,27	-0.169	0.036		
Smoking (1 = Yes)	0,05	0,376	0,89	-0.055	0.147		
Classification (1 = white-collars)	-0,01	0,848	-0,19	-0.116	0.095		
WHOQOL-bref social relationship domain						0,146	0,111
Workload	-0,03	0,623	-0,49	-0.162	0.097		
Job Insecurity	-0,06	0,301	-1,03	-0.180	0.056		
N. of diseases	-0,07	0,223	-1,22	-0.189	0.044		
Job Autonomy	-0,03	0,627	-0,49	-0.160	0.096		
Physical activity level (1 = medium – high)	0,05	0,414	0,82	-0.068	0.164		
Emotional Exhaustion	-0,29	0,000	-4,25	-0.429	-0.158		
Sex (1 = M)	-0,03	0,615	-0,50	-0.156	0.092		
Age (yrs.)	-0,15	0,011	-2,54	-0.265	-0.034		
Smoking (1 = Yes)	0,11	0,057	1,91	-0.003	0.225		
Classification (1 = white-collars)	-0,04	0,569	-0,57	-0.155	0.085		
Indirect effects							
Workload	-0,12	0,000	-3,826	-0.188	-0.061		
Job Insecurity	-0,03	0,084	-1,728	-0.062	0.004		
N. of diseases	-0,03	0,075	-1,778	-0.063	0.003		
Job Autonomy	0,10	0,001	3,555	0.044	0.153		
Physical activity level (1 = medium – high)	0,03	0,048	1,978	0.000	0.067		
Total Effects							
Workload	-0,15	0,008	-2,632	-0.274	-0.040		
Job Insecurity	-0,11	0,138	-1,485	-0.212	0.029		
N. of diseases	-0,09	0,092	-1,683	-0.222	-0.017		
Job Autonomy	0,07	0,287	1,066	-0.056	0.190		
Physical activity level (1 = medium – high)	-0,02	0,174	1,359	-0.036	0.200		

Table 12: Model 3 – impact of the included variables on the WHOQOL-bref – social relationship domain

In model 4 we investigated the effects of the selected variables on the social relationship domain (**Table 13**). The roles of WL (β = 0.42, 95% C.I. (0.329, 0.507), p < 0.0001), JA (β = −0.11, 95% C.I. (−0.212, −0.012), p < 0.029) and medium-to-high PA level (β = −0.11, 95% C.I. (−0.212, −0.012), p=0.029) significantly affected EE, which had a negative relationship with QoL (β = −0.25, 95% C.I. (−0.379, −0.115), p < 0.0001). We observed a full mediation for WL and PA, while JA still maintained a positive impact, even borderline, on QoL (β = 0.12, 95% C.I. (0.000, 0.247), p = 0.050).

n = 255	β	p-value	z-value	95% C.I.		R^2	R^2 - adj
Exhaustion						0,337	0,313
Workload	0,42	0,000	9,17	0.329	0.507		
Job Insecurity	0,10	0,058	1,90	-0.003	0.202		
N. of diseases	0,10	0,061	1,88	-0.004	0.200		
Job Autonomy	-0,34	0,000	-6,81	-0.436	-0.241		
Physical activity level (1 = medium – high)	-0,11	0,029	-2,19	-0.212	-0.012		
Sex (1 = M)	0,01	0,822	0,23	-0.097	0.122		
Age (yrs.)	-0,06	0,234	-1,19	-0.165	0.040		
Smoking (1 = Yes)	0,06	0,288	1,06	-0.046	0.156		
Classification (1 = white-collars)	-0,01	0,899	-0,13	-0.113	0.099		
WHOQOL-bref environmental domain						0,197	0,164
Workload	-0,10	0,132	-1,51	-0.220	0.029		
Job Insecurity	-0,18	0,002	-3,16	-0.293	-0.069		
N. of diseases	-0,07	0,223	-1,22	-0.184	0.043		
Job Autonomy	0,12	0,050	1,96	0.000	0.247		
Physical activity level (1 = medium – high)	-0,03	0,616	-0,50	-0.141	0.084		
Emotional Exhaustion	-0,25	0,000	-3,66	-0.379	-0.115		
Sex (1 = M)	0,05	0,386	0,87	-0.067	0.173		
Age (yrs.)	-0,02	0,737	-0,34	-0.133	0.094		
Smoking (1 = Yes)	-0,05	0,406	-0,83	-0.159	0.064		
Classification (1 = white-collars)	-0,02	0,794	-0,26	-0.132	0.101		
Indirect effects							
Workload	-0,10	0,001	-3,367	-0.163	-0.043		
Job Insecurity	-0,03	0,092	-1,686	-0.053	0.004		
N. of diseases	-0,02	0,096	-1,667	-0.052	0.004		
Job Autonomy	0,08	0,001	3,199	0.032	0.135		
Physical activity level (1 = medium – high)	0,03	0,061	1,871	-0.001	0.057		
Total Effects							
Workload	-0,10	0,001	-3,367	-0.310	-0.088		
Job Insecurity	-0,03	0,092	-1,686	-0.319	-0.092		
N. of diseases	-0,02	0,096	-1,667	-0.210	0.020		
Job Autonomy	0,08	0,001	3,199	0.092	0.322		
Physical activity level (1 = medium – high)	0,03	0,061	1,871	-0.115	0.113		

Table 13: Model 4 – impact of the included variables on the WHOQOL-bref – environmental domain

3.2.2.3. Discussion

The results of this second investigation provided a picture of the perception of QoL and work-related factors among an Italian workers' population. Interestingly, the identification of three subgroups according to the different QoL levels allowed the highlighting of significant differences in both personal (age and n. of diseases) and work-related (Workload, Emotional Exhaustion, Job Insecurity, and Job Autonomy) characteristics. Moreover, Emotional Exhaustion was found to have an important role in reducing the QoL perception, mediating also the role of factors non-related to the working activity, such as the PA level.

Even though only a few studies investigated the relationship between QoL and burnout, a growing literature has demonstrated the negative association between them (Moraes, Hitora, and Verardi 2019; Colby et al. 2018; Naz, Hashmi, and Asif 2016). Specifically, individuals having a great vulnerability to burnout were found to have lower scores in all QoL domains (WHOQOL-bref) in comparison to the rest of the population, with the lowest scores in the psychological domain (Moraes, Hitora, and Verardi 2019). Concerning work-related factors, we observed that the individuals with better scores are those classified in the high QoL subgroup, highlighting, once more,

that the individual's perceptions of the working context could strongly influence the workers' professional and personal lives and affect the subjective evaluation of QoL (Moraes, Hitora and Verardi 2019). Poor working conditions, indeed, such as those resulting from the combination of high job demands and low job resources, or from the workers' scarce effectiveness in dealing with their job demands, represent a fertile ground for burnout development (de Vries and Bakker 2022). Several organisational factors have been thus far identified to be able to play a role in burnout development, increasing the risk (such as work overload, lack of innovation, stimulation, and autonomy, negative interpersonal relationships, bureaucratic pressures and lack of feedback, night shifts) or as protective factors (job satisfaction, leadership, benefits and organizational policies are essential elements of professional achievement) (Moraes, Hitora, and Verardi 2019; Naz, Hashmi, and Asif 2016). Even though it seems unintuitive, the working years were reported to have a negative association with burnout. Indeed, as observed by Naz and colleagues in a sample of nurses, individuals with higher seniority may have learnt the ability to cope with the situation and have become more resilient, resulting less prone to burnout (Naz, Hashmi, and Asif 2016).

Specifically, our analysis revealed that workload had a significant impact on Emotional Exhaustion, which, in turn, completely mediated the role of this stressor on QoL. This result is in line with previous findings reported in the literature, suggesting that work overload can reduce the workers' ability to meet job demands due to the lack of opportunity to rest, recover, and restore balance (Maslach and Leiter 2016).

Several strategies have been proposed to enhance the workers' ability to deal with this condition, including the implementation of healthy lifestyles in order to improve the ability to recover through better sleep, exercise, and nutrition, resulting in the reduction of exhaustion (Maslach and Leiter 2016). Our results, specifically, strengthened the role of PA, highlighting its role in reducing emotional exhaustion and promoting QoL. These results become even more valuable in the light of the results of studies carried out during the pandemic, undeniably demonstrating the role of PA in promoting well-being (Violant-Holz et al. 2020).

Specifically, concerning the working environment, the beneficial effect of PA on the prevention and treatment of burnout syndrome is well-documented (Ochentel, Humphrey, and Pfeifer 2018).

Whereas the frequent exposure to high physical job demands may be detrimental (a phenomenon known as the "*physical activity paradox*"), off-job PA (*i.e.*, those activities performed during transportation, household chores and gardening, and leisure activities) may be effective in ensuring the recovery, *i.e.* in the generation of useful resources (energetic, physical, and cognitive) to manage present and future workday challenges and to prevent the accumulation of physiological and psychological burdens leading to burnout (de Vries and Bakker 2022). Indeed, off-job PA is often characterised by a higher intensity and a shorter duration and can be tailored according to individual's needs and abilities (Holtermann et al. 2021).

The physiological and psychological changes which can be tributed to the regular practice of PA are numerous and can be related to the positive effects in both preventing burnout and improving QoL. Indeed, PA can (i) represent a behavioural distraction from stressful situations; (ii) foster the development of mastery and self-efficacy perceptions, reducing the sensitivity to negative stimuli; (iii) reduce the physiological sensitivity to chronic stress and improve the ability to deal with stress at work without being physiologically overwhelmed by it; (iv) guarantee a faster physical recovery after stressful situations; (v) reduce anxiety and improving emotional well-being (Ochentel, Humphrey, and Pfeifer 2018).

The strength of this study relies on the high number of subjects invited to answer the questionnaire, leading to the possibility to obtain a clear picture of the QoL level and of those variables variously able to play a role in determining QoL in the Italian working population investigated. Despite the cross-sectional study design, the simultaneous assessment of several

variables belonging to different domains (socio-demographic factors, QoL, lifestyle, and work-related factors) allowed us to investigate the possible pathway through which some of these elements can influence each other. Specifically, the exhaustion resulted to be a powerful mediator of the QoL, when considered in association with these variables. The identification of different subgroups according to their QoL seemed useful in the identification of those subjects with more difficulties. This approach could be useful in eventual data collection aiming to define strategies and programs to promote workers' well-being. The main limitations consist instead in the cross-sectional design, not allowing to identify some causal relationship among variables, in the difficulties in the quantification of the PA by questionnaires, leading to a lot of missing data concerning this domain, and in the lack of multiple settings, preventing to generalise the results observed. Moreover, the anonimyty of the survey answers prevented the investigation of a possible selection bias, resulting in a over/underestimation of the observed relationships.

3.3. Living Environment

3.3.1. Study Line 3: Health Promotion during Pregnancy

3.3.1.1. Aim

The aim of the study is to assess the benefits of the PA administration during pregnancy to counterbalance the oxidative and inflammatory burden typical of this stage, with a particular focus on obese women. The simultaneous assessment of lifestyle factors and QoL would allow to observe eventual benefits of the intervention in pregnant women' wellbeing.

3.3.1.2. Study Design

Measurements were performed three times during pregnancy: the first (T1) at the boundary between the first and the second trimester (12-15 weeks), the second (T2) at the boundary between the second and the third trimesters (24-28 weeks), and the third (T3) at the end of the third trimester (37-38 weeks). The samplings were performed at the S. Anna Hospital (Turin), in occasion of routinary monitoring visits. Each subject accepting to participate signed out a written informed consent and during the sampling day was interviewed to complete a questionnaire, underwent the assessment of weight, and provided a spot urine sample to the oxidative and inflammatory profile evaluation. Data and samples were pseudonymised immediately after collection assigning an alphanumerical string to each subject.

3.3.1.3. Epidemiological Sample and Recruitment

The epidemiological sample was represented by pregnant women recruited in occasion of routinary follow-ups at the Sant'Anna Obstetric Gynecological Hospital (*Azienda Ospedaliera Città della Salute e della Scienza – Turin*). Women recruited were divided into two groups according to their BMI: owerweight and obese (OWO) and normal weight (non-OWO). The intervention was randomly assigned to the subjects, determining the split of each group in subjects performing PA (Active) and non-performing PA (non-Active). Subjects in the active group were gifted with a fit ball, useful for the training lessons. The inclusion criteria were: (i) the recruitment before the 15^{th} gestational weeks, (ii) the absence of pathological condition with an inflammatory pathway, (iii) being Italian-speaking subjects.

3.3.1.4. Questionnaire

The questionnaire was administered by an interviewer to collect information about socio-demographic characteristics (age, working activity, and education), and QoL, as previously described.

3.3.1.4.1. WHOQOL-bref

(as described for *Study Line 1*)

3.3.1.4.2. International Physical Activity Questionnaire (IPAQ)

(as described for *Study Line 1*)

3.3.1.5. Bio-molecular Profile assessment

The bio-molecular profile was assessed in spot urine samples collected during the sampling day, kept refrigerated, aliquoted and stored at −80°C until analysis.

3.3.1.5.1. 15-F2t-Isoprostane

(as described for *Study Line 1*)

3.3.1.5.2. Total Antioxidant Power

(as described for *Study Line 1*)

3.3.1.5.3. Cytokine concentration

In *Study Line 3* the urinary cytokine concentration was measured with the Bio-Plex Pro Human Cytokine 8-plex Assay (BIO-RAD, CA, USA), according to the manufacturer's instructions. The panel allows the simultaneous measurements of GM-CSF, IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α. The panel was customised enabling the addition of MCPH-1.

The Bio-Plex multiplex immunoassay system employs xMAP technology (Luminex) to allow the multiplexing of up to 100 different assays in a single sample, employing different beads sets distinctly coloured using two fluorescent dyes at distinct ratios. In this technology, each analyte is bind by two antibodies, one linked to a set of beads with a same colour, the other to a fluorescent reported dye label. The use of beads with different colours enables the simultaneous detection of various analytes in the same sample. The detection is based on a dual flow cytometer, sorting out the different assays by bead colours in one channel and determining the analyte concentration by quantify the reporter dye fluorescence in the other channel.

To perform the assay all the diluents and buffers were equilibrated to room temperature, while vials containing beads, the Detection Antibody, Controls, Standards, and Streptavidin-PE were kept in ice until use.

The thawed samples were centrifuged for 15 minutes at 1000xg at 4°C, and directly in the assay without being diluted. 65 µL of each sample were transferred in a white plate following the scheme in **Figure 24:**

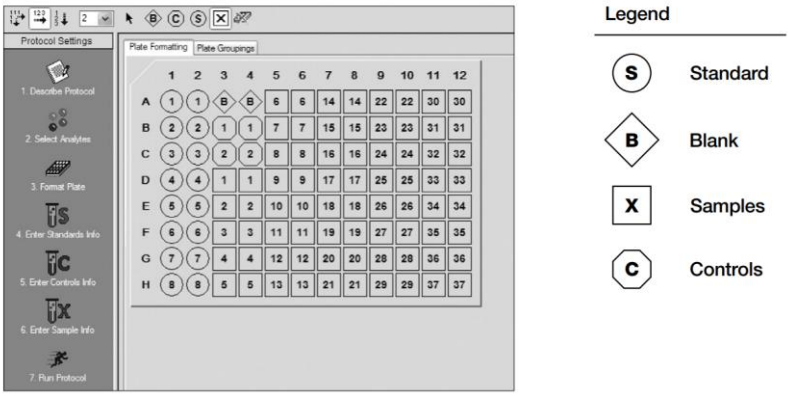


Figure 24: Standards, samples, and controls disposition in the plate.

Standard and controls were reconstituted by adding in each vial 250 µL of the Standard Diluent, vortexed for 5 seconds to enable a proper mixing, and incubated in ice for exactly 30 minutes. Within this period of time beads were vortexed for 30 seconds at medium speed and diluted in an aluminate vial to 1X with 4845 µL of the Assay Buffer, following the following doses (**Figure 25**):

Premixed Panels

# of Wells	10x Beads, µl	Assay Buffer, µl	Total Volume, µl
96	570	5,130	5,700

Singleplex Assays

# of Wells	Singleplex #1 and #2 20x Beads, µl	Assay Buffer, µl	Total Volume, µl
96	285	5,130	5,700

Note: 20x singleplex beads allow multiplexing up to 20 analytes.

Figure 25: Beads preparation

Beads were than vortexed and 50 µL of the mixture were transferred in each well of the black plate. Each well was then automatedly washed with 100 µL of the Wash Buffer 1X (obtained diluting the Wash Buffer 10X with 540 mL of dH_2O. The washing step was repeated for a total of two washing.

At the end an eight-point standard curve was prepared by a 1:4 dilution series, as displayed in **Figure 26**.

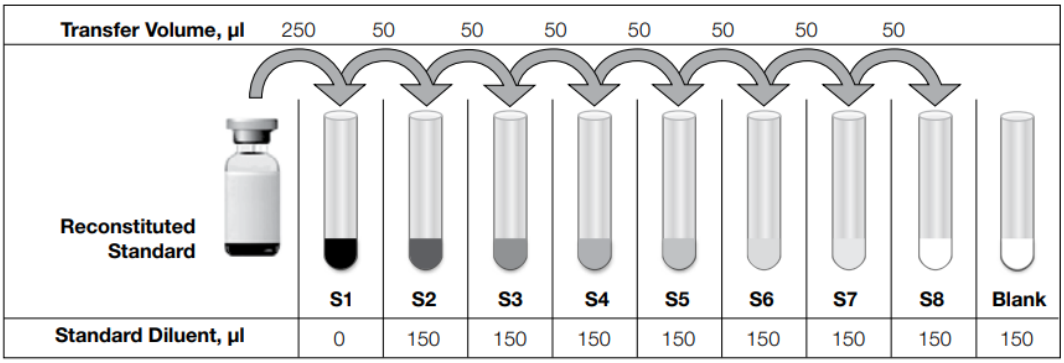


Figure 26: Standard Curve preparation

Standards and controls were vortexed and transferred in the white plate, then 50 µL of Standards, Samples, and controls were transferred in the black plate containing the beads. The plate was sealed with an aluminated sealing tape and incubated for 30 minutes on an orbital microplate shaker at 850 ± 50 rpm a room temperature. Ten minutes before the end of the incubation the Detection Antibodies were vortexed for 5 seconds and diluted with 2550 µL of Detection Antibody Diluent, following the scheme in **Figure 27**:

Premixed Panels

# of Wells	10x Detection Ab, µl	10x Detection Ab Diluent HB, µl	Total Volume, µl
96	300	2,700	3,000

Singleplex Assays

# of Wells	Singleplex #1 and #2 20x Detection Ab, µl	Detection Ab Diluent HB, µl	Total Volume, µl
96	150	2,700	3,000

Note: 20x singleplex beads allow multiplexing up to 20 analytes.

Figure 27: Detection Antibody preparation

At the end of the incubation, each well was then automatedly washed with 100 µL of the Wash Buffer 1X for a total of three times, and then filled with 25 µL of Detection Antibody. The plate, sealed with an aluminated sealing tape, was incubated 30 minutes on the orbital microplate shaker at 850 ± 50 rpm a room temperature, and then washed as previously described. Ten minutes before the incubation end, the Streptavidin-PE 1X was prepared following the scheme in **Figure 28** and kept protected from light:

# of Wells	100x SA-PE, µl	Assay Buffer, µl	Total Volume, µl
96	60	5,940	6,000

Figure 28: Streptavidin-PE 1X preparation

Each well was filled with 50 µL of the Streptavidin-PE 1X, and then the plate was newly sealed with the aluminated sealing tape, incubated 10 minutes on the orbital microplate shaker at 850 ± 50 rpm at room temperature, and washed, as previously described.

At the end the beads were resuspended in 125 µL of Assay Buffer, and newly incubated as before for 30 seconds. At the end the plate was read by the Bio-Plex 200 (BIO-RAD, CA, USA). The quantification of the analyte concentration was calculated by the Bio-Plex Manager software (BIO-RAD, CA, USA) basing on the standard curve provided for each analyte.

3.3.1.6. Body Mass Index

The Body Mass Index (BMI) was calculated by the following formula:

$$BMI = \frac{Weight\ (Kg)}{[Height\ (m)]^2}$$

In *Study Lines 1 and 3*, weight was measured by a segmental body composition scale (TANITA BC-545N, Amsterdam, The Netherlands) at all three times, while in *Study Line 2* was referred.
The height of each subject was measured by an altimeter (Seca, Hamburg, Germany) at the T0 in *Study Line 1*, while was reffered in both *Study Lines 2 and 3*.

3.3.1.7. Physical Activity Administration Protocols

The administration was web-based, to deal with both pandemic restrictions and maximise the compliance of volunteers taking part to the project.

In *Study Line 3* the administration of PA wasprovided by web meetings, in order to allow a higher compliance due to the possibility to attend to the training lessons from home. Lessons of PA were held by a skilled trainer. Each subject was proposed to participate in two 1-hour weekly sessions, tailored according to the needs and medical indications of each subject.

Each lesson was organised as follows: i) general warm-up exercises (10-15 min), ii) mobilisation exercises (10-25 min), iii) leg circuit workout, iv) arm circuit workout, v) cool-down exercises.

3.3.1.8. Statistical analysis

Statistical analyses were performed by SPSS Statistics 28 (IBM SPSS Statistics, New York, NY, USA). Graphs were created by R Studio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA).

Categorical variables have been reported as frequency (n) and percent (%) and compared by the χ squarewd test, while continuous variables have been reported as median and interquartile range (IQR). Wilcoxon's Signed-Rank Test or Kruskal-Wallis test were employed to compare ordinal data and continuous variables. The Cronbach α was calculated for WHOQOL-bref questionanires and for work-related factors scales (Workload, Exhaustion, Job Insecurity and Job Autonomy).

Specifically, the comparisons across the different times were performed by the Friedman test. Since the data are preliminar and the sampling is still ongoing, we did not perform comparisons among groups and we limited our analyses to the observation of the change in QoL scores and biomarkers concentration at the three sampling points. Concerning the inflammatory panel, several measurements were Out of Range (OOR), and below asymptote of the equation. We thus focus our analyses on MCP-I, IL-6, IL-8 (having less then 10% of measurements OOR at each sampling point) and IL-10 (having less than 40% of values OOR at each sampling point).

3.3.2. Results

The epidemiological sampleinvolved in this study is random sample and its characteristics of are displayed in **Tables 14-17**, according to the training administration in the different groups (OwO and Controls).

Obese			
	w/o PA administration	*w/ PA administration*	**w/o PA vs w/PA**
	n (%)	*n (%)*	**p-value**
Nationality			0.619
Italian	12 (92.3%)	8 (100.0%)	
Foreign	1 (7.7%)	0 (0.0%)	
Education			0.325
Middle school license	5 (38.5%)	1 (12.5%)	
High-school license	5 (38.5%)	3 (37.5%)	
Degree	3 (23.1%)	4 (50.0%)	
Working activity			0.029
Unemployed	10 (76.9%)	2 (25.0%)	
Employed	3 (23.1%)	6 (75.0%)	
Health status			0.596
No	7 (53.8%)	5 (62.5%)	
Diabetes	1 (7.7%)	0 (0.0%)	
Hypertension	2 (15.4%)	0 (0.0%)	
Cardiovascular disorders	1 (7.7%)	1 (12.5%)	
Thyroid disorders	1(7.7%)	0 (0.0%)	
Smoking (n. cigarette/die) – 3 months before pregnancy			0.205
No	6 (50.0%)	4 (50.0%)	
<1	0 (0.0%)	2 (25.0%)	
2-5	0 (0.0%)	1 (12.5%)	
6-10	2 (16.7%)	1 (12.5%)	
11-20	3 (25.0%)	0 (0.0%)	
21-40	1 (8.3%)	0 (0.0%)	

Tab 14: Characteristics of the subjects enrolled in the obese group (*w/o = without; w/ = with*).

Obese					
w/o PA administration					
	Median (IQR)				
Gestational age (weeks)	15 (5)				
Age (years)	31 (16)				
N. children	1 (1)				
	T1	**T2**	**T3**	**T1 vs T2 vs T3**	**T1 vs T3**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p-value*	*p-value*
WHOQOL-bref – physical domain	14.29 (2.29)	14.29 (2.14)	14.00 (4.57)	n.s.	n.s.
WHOQOL-bref – psychological domain	14.00 (3.00)	13.67 (3.67)	15.00 (3.00)	n.s.	n.s.
WHOQOL-bref – social relationship domain	16.00 (3.33)	16.67 (3.67)	16.00 (2.67)	n.s.	**0.042**
WHOQOL-bref – environmental domain	13.00 (1.75)	12.50 (2.00)	13.75 (2.63)	n.s.	n.s.
WHOQOL-bref – overall domain	16.00 (3.00)	14.00 (2.00)	16.00 (1.00)	n.s.	
IsoP [ng/mg crea]	7.39 (2.46)	6.34 (3.78)	11.20 (10.16)	n.s.	0.007
MDA [umol/mmol crea]	0.11 (1.13)	0.08 (0.11)	0.15 (0.23)	n.s.	n.s.
TAP	2.43 (3.18)	3.10 (2.83)	3.49 (2.34)	n.s.	n.s.
MCP-1 (ng/mg crea]	48.52 (51.25)	-	227.20 (294.29)	-	**0.028**
IL-6 [ng/mg crea]	0.33 (2.28)	-	4.59 (8.44)	-	n.s.
IL-8 [ng/mg crea]	3.89 (20.26)	-	4.86 (31.33)	-	n.s.
IL-10 [ng/mg crea]	0.77 (1.32)	-	0.67 (1.93)	-	-

Tab 15a: Characteristics of the subjects enrolled in the obese group not attending the exercise training.

Obese					
w/ PA administration					
	Median (IQR)				
Gestational age (weeks)	11.5 (3)				
Age (years)	34.5 (7)				
N. children	1 (1)				
	T1	**T2**	**T3**	**T1 vs T2 vs T3**	**T1 vs T3**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p-value*	*p-value*
WHOQOL-bref – physical domain	14.57 (6.29)	14.29 (3.71)	14.57 (5.00)	n.s.	n.s.
WHOQOL-bref – psychological domain	12.73 (3.83)	12.67 (1.17)	13.33 (0.83)	n.s.	n.s.
WHOQOL-bref – social relationship domain	16.00 (2.33)	16.67 (5.67)	14.00 (4.67)	n.s.	n.s.
WHOQOL-bref – environmental domain	14.75 (2.88)	14.25 (1.38)	13.64 (2.50)	n.s.	n.s.
WHOQOL-bref – overall domain	14.00 (6.00)	16.00 (2.00)	16.00 (3.00)	**0.016**	**0.014**
IsoP [ng/mg crea]	5.45 (2.25)	6.03 (4.01)	6.82 (7.56)	n.s.	n.s.
MDA [umol/mmol crea]	0.09 (0.12)	0.22 (0.54)	0.10 (0.18)	n.s.	n.s.
TAP	3.36 (1.91)	2.61 (2.00)	3.31 (3.96)	n.s.	n.s.
MCP-1 (ng/mg crea]	64.14 (92.18)	-	110.60 (190.13)	-	n.s.
IL-6 [ng/mg crea]	0.17 (3.58)	-	0.97 (4.86)	-	n.s.
IL-8 [ng/mg crea]	7.46 (168.69)	-	18.24 (94.43)	-	n.s.
IL-10 [ng/mg crea]	1.92 (0.0)	-	0.37 (0.33)	-	-

Tab 15b: Characteristics of the subjects enrolled in the obese group attending the exercise training.

Controls			
	w/o PA administration	*w/ PA administration*	**w/o PA vs w/PA**
	n (%)	*n (%)*	**Yes vs No**
Nationality			0.178
Italian	8 (80.0%)	13 (100.0%)	
Foreign	2 (20.0%)	0 (0.0%)	
Education			0.367
Middle school license	0 (0.0%)	0 (0.0%)	
High-school license	3 (30.0%)	2 (15.4%)	
Degree	7 (70.0%)	11 (84.6%)	
Working activity			0.398
Unemployed	2 (20.0%)	1 (7.7%)	
Employed	8 (80.0%)	12 (92.3%)	
Health status			0.687
No	6 (60.0%)	8 (61.5 %)	
Diabetes	0 (0.0%)	1 (7.7%)	
Hypertension	1 (10.0%)	2 (15.4%)	
Cardiovascular disorders	0 (0.0%)	0 (0.0%)	
Thyroid disorders	2 (20.0%)	2 (15.4%)	
Depression	1 (10.0%)	0 (0.0%)	
Smoking (n. cigarette/die) – 3 months before pregnancy			
No	9 (90.0%)	9 (69.2%)	
<1	0 (0.0%)	2 (15.4%)	
2-5	0 (0.0%)	1 (7.7%)	
6-10	0 (0.0%)	1 (7.7%)	
11-20	1 (10.0%)	0 (0.0%)	
21-40	0 (0.0%)	0 (0.0%)	

Tab 16: Characteristics of the subjects enrolled in the control group.

Controls					
w/o PA administration					
	Median (IQR)				
Gestational age (weeks)	13 (4)				
Age (years)	32.50 (6)				
N. children	0 (1)				
	T1	**T2**	**T3**	**T1 vs T2 vs T3**	**T1 vs T3**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p-value*	*p-value*
WHOQOL-bref – physical domain	14.86 (3.43)	15.14 (2.57)	15.14 (1.57)	n.s.	n.s.
WHOQOL-bref – psychological domain	15.33 (4.33)	15.00 (2.50)	14.67 (2.50)	n.s.	n.s.
WHOQOL-bref – social relationship domain	16.00 (2.67)	18.00 (5.00)	16.00 (3.67)	n.s.	n.s.
WHOQOL-bref – environmental domain	15.00 (1.25)	14.75 (1.38)	14.00 (0.95)	n.s.	n.s.
WHOQOL-bref – overall domain	16.00 (2.00)	17.00 (3.50)	16.00 (2.00)	n.s.	n.s.
IsoP [ng/mg crea]	5.53 (5.23)	6.11 (2.22)	6.66 (5.51)	n.s.	n.s.
MDA [umol/mmol crea]	0.12 (0.12)	0.05 (0.14)	0.10 (0.15)	n.s.	n.s.
TAP	4.57 (2.88)	3.56 (2.95)	3.46 (1.81)	n.s.	n.s.
MCP-1 (ng/mg crea]	139.17 (308.90)	-	196.37 (440.40)	-	n.s.
IL-6 [ng/mg crea]	3.76 (5.36)	-	5.74 (10.12)	-	n.s.
IL-8 [ng/mg crea]	2.17 (8.16)	-	2.59 (77.45)	-	n.s.
IL-10 [ng/mg crea]	1.38 (3.31)	-	1.75 (2.60)	-	n.s.

Tab 17a: Characteristics of the subjects enrolled in the control group not attending the exercise training.

Controls					
w/ PA administration					
	Median (IQR)				
Gestational age (weeks)	14 (4)				
Age (years)	37.0 (4)				
N. children	1 (1)				
	T1	**T2**	**T3**	**T1 vs T2 vs T3**	**T1 vs T3**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	*p-value*	*p-value*
WHOQOL-bref – physical domain	14.57 (4.71)	16.00 (4.29)	14.86 (6.28)	n.s.	n.s.
WHOQOL-bref – psychological domain	14.00 (4.17)	15.33 (2.33)	15.33 (3.33)	n.s.	n.s.
WHOQOL-bref – social relationship domain	16.00 (2.00)	14.67 (4.67)	17.33 (6.00)	n.s.	n.s.
WHOQOL-bref – environmental domain	13.75 (4.00)	14.50 (4.50)	14.00 (3.00)	n.s.	n.s.
WHOQOL-bref – overall domain	16.00 (4.00)	16.00 (2.00)	16.00 (4.00)	n.s.	n.s.
IsoP [ng/mg crea]	6.20 (3.96)	6.19 (5.58)	6.55 (2.95)	n.s.	n.s.
MDA [umol/mmol crea]	0.06 (0.27)	0.06 (0.10)	0.10 (0.17)	n.s.	n.s.
TAP	3.18 (2.36)	3.36 (1.42)	3.50 (2.71)		n.s.
MCP-1 (ng/mg crea]	140.70 (92.18)	-	292.38 (307.93)	-	**0.021**
IL-6 [ng/mg crea]	1.48 (2.61)	-	6.21 (4.66)	-	**0.028**
IL-8 [ng/mg crea]	8.41 (26.28)	-	19.29 (39.39)	-	n.s.
IL-10 [ng/mg crea]	0.92 (1.74)	-	0.65 (1.58)	-	n.s.

Tab 17b: Characteristics of the subjects enrolled in the control group attending the exercise training.

Concerning the bio-molecular profile assessment (**Figure 29 and 30**), the comparisons among measures obtained at the different sampling points revealed a significant increase in MCP-1 in both obese and control women not attending the training. In this last group we observed also a significant increase in IL-6 at the end of the pregnancy. Concerning QoL (**Figure 31**), in obese women, we observed a significant increase in the social relationship domain in those not performing PA and a significant increase in the overall QoL in those attending the training lessons.

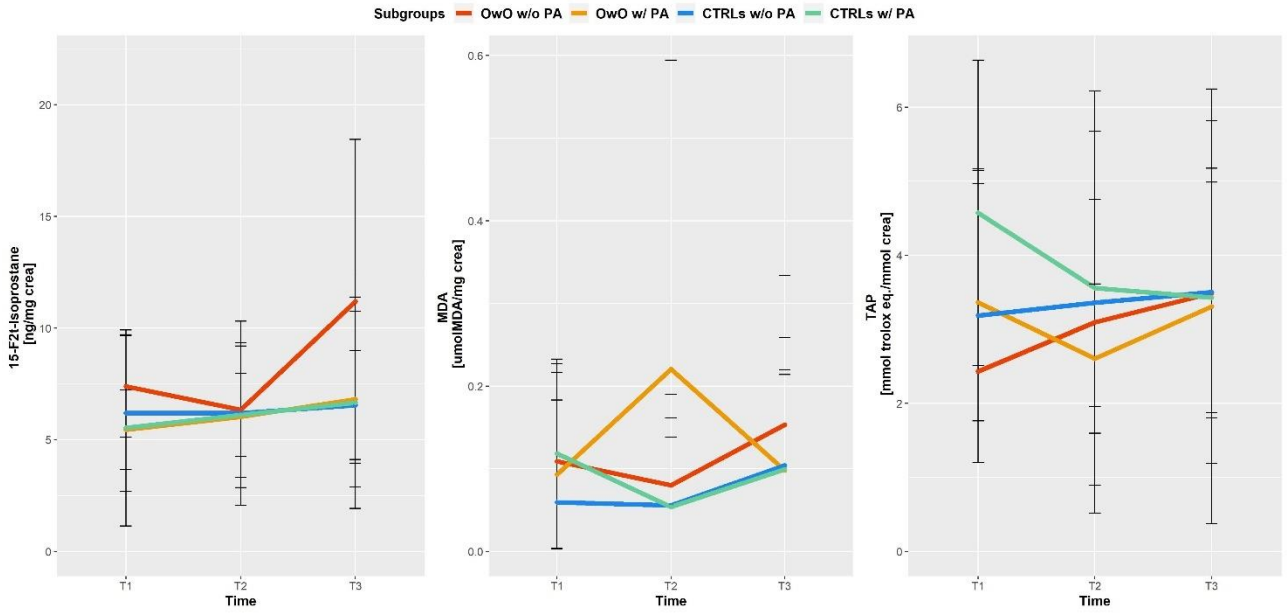


Figure 29: Biomolecular profile among the four groups – oxidative status

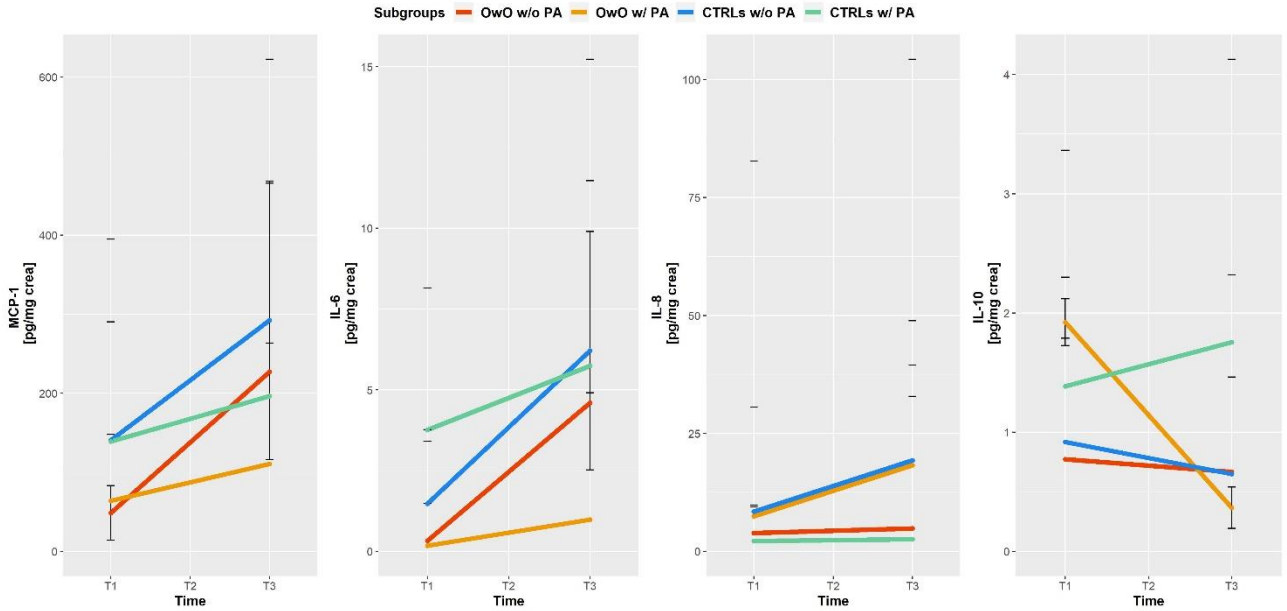


Figure 30: Biomolecular profile among the four groups – inflammatory status

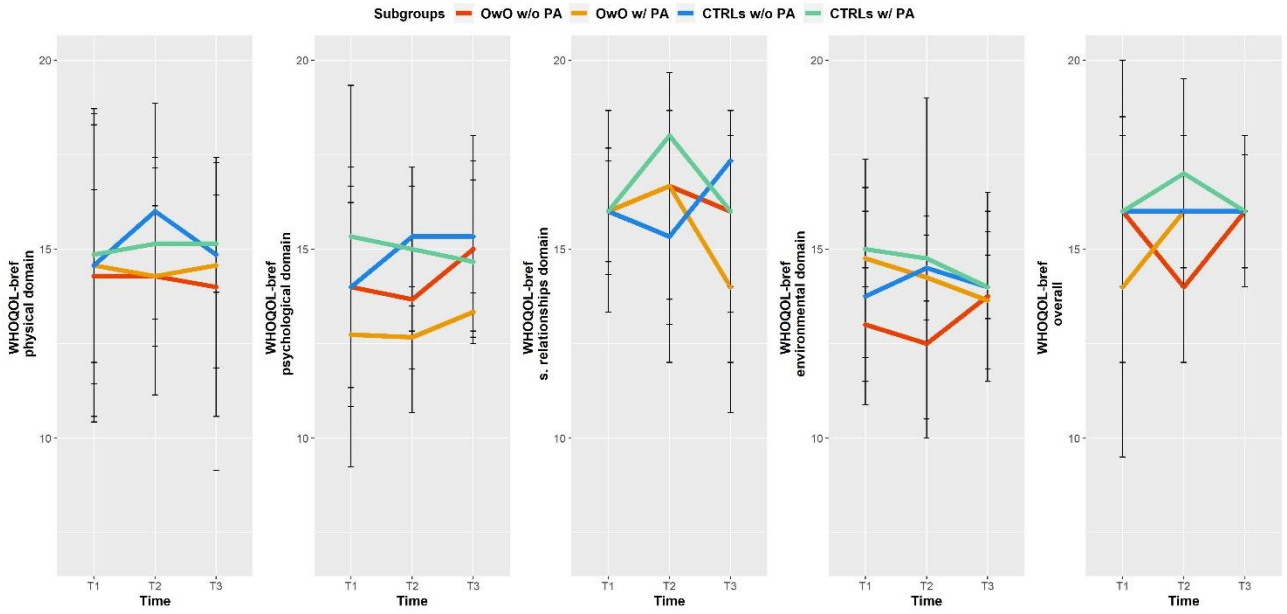


Figure 31: QoL among the four groups

3.3.3. Discussion

The aim of the present study line was to investigate the possible beneficial role of the administration of a training program involving a sample of pregnant women to observe if this intervention could be useful in limiting the physiological increase in oxidative and inflammatory burdens and in shaping the QoL. Since the women's weight at the beginning of the pregnancy is a critical element well-known to be related to possible negative health outcomes, and being obesity characterised by higher levels of oxidative stress and inflammation in comparisons with normal-weight subjects, we decided to enroll both obese and normal weight women and randomly assign the training to the participants in each group. Since the enrollment is still ongoing, the data reported are preliminary and we decided to limit our investigation to the analysis of eventual differences across the pregnancy in the four subgroups. We instead decided to not perform comparisons among the different subgroups. The small number of subjects resulted in a high scattering of the data, revealing a high interindividual variability, especially in the biomarkers. However, even if no sgnificance have been highlighted and the comparisons among groups have not been performed due to the small number of subjects in each group, the analysis of the visual trend in both QoL and biomarkers revealed some interesting elements, which seems worth to be further investigated in larger samples. More specifically, concerning PA, the controls seem to have higher QoL scores than obese subjects, while in all subgroups the values at T2 seem to represent a sort of inflection point, in line with the literature (Boutib et al. 2022; Nascimento et al. 2011). These relationships could be related also to a different socio-economic position, as potentially suggested by the significant difference observed in the education level (Zhan, Su, and Chang 2022).

Concerning biomarkers, the plots revealed some interesting patterns. Particularly interesting are the trends of 15-F2t-IsoP and TAP. Indeed, if the dramatic increase in 15-F2t-IsoP between T2 and T3 only in obese subjects not attending the training lessons were confirmed, we could assume that in these women performing regular exercise is effective in controlling the oxidative burst associated with the third trimester (Palm et al. 2009). The TAP seems to have different behaviour: indeed, while there seems to be a huge variability at the T1, at the end of the pregnancy the values seem to converge to a similar level, independently from the starting point. Moreover, in subject attending the training lessons, there seem to be a more pronounced reduction in the biomarker

concentration among T1 and T2, apparently in line with the literature, even if it should be confirmed in a larger sample (Hussain et al. 2021). Concerning the inflammatory profile, PA seems to have a role in preventing the rise of MCP-1 concentration in both obese and control subjects and, as well, in limiting the increase in IL-6 in obese women, apparently in contrast with what was observed in the literature (Goudreau et al. 2021; van Poppel et al. 2014). These preliminary results seem to support the effectiveness of pregnancy-specific PA programs to promote health and well-being in this peculiar condition. If confirmed, these results could contribute to raising awareness on the topic, leading to further stress on the urgency of the implementation of specific programs tailored to the specific needs of pregnant women.

The main strength of this study consists in the simultaneous investigation of several biomarkers in urine samples, in order to assess the effectiveness of a training program on the biomolecular profile. If further analysis will confirm our hypothesis, the results of this study would strengthen the beneficial role of PA during pregnancy, the administration of tailored workout programs could be suggested as part of prevention strategies to promote the adoption of healthy lifestyles during this delicate period, which could affect both the mother and the fetus health. The main limitation consists, instead, at least at the present moment, of the small number of subjects, resulting in the impossibility of properly evaluating the effects investigated and to discriminate outliers in the data due to a huge interindividual variability. Moreover, the analysis of biomarkers in urine specimens prevented a more comprehensive analysis of the inflammatory profile.

4. Conclusions

The way work and its characteristics have evolved over time, particularly in the last few decades. Indeed, in the recent past, we have assisted in the creation of several new jobs and in huge modifications to most of those already existing, even though their organisation and management often convey an old-fashioned approach (Litchfield et al. 2016). Consequently, the interest in promoting the health of workers has become more and more crucial, with particular attention to the well-being and QoL of workers.

Psychological and social aspects of work (Michie and Williams 2003; Enns et al. 2016; Joyce et al. 2016) can also have a role in the aetiology of mental health disorders, resulting in possible targets for intervention in the workplace. High levels of job strain (*i.e.*, low decision latitude and high demands), low levels of social support at work, job insecurity, discrimination, and perceived imbalances between job efforts and rewards are linked to common mental disorders like depression and anxiety and, more in general, with lower psychological well-being (Stansfeld and Candy 2006; Theorell et al. 2015; Schütte et al. 2014; Niedhammer et al. 2013). Conversely, higher levels of job control, social support, and job security are associated with being free of disorders and flourishing mental health (Fan et al., 2019).

The results obtained in the different study lines, even in the case of preliminary results, highlighted the broad range of situations and scenarios where it would be worth to investigating the relationship between the QoL and the bio-molecular profile, especially from a health promotion perspective.

Indeed, to promote health and safety and address disparities, QoL and biomarkers of oxidative stress and inflammation seems to be promising instruments for the early identification of subjects needing special attention. The main challenge is represented by the identification of a valid array of indicators, biological and self-reported, sensitive to both the derangements from physiological conditions and their restoration due to stress reduction, possibly involving matrices not involving invasive sampling.

Further studies would be desirable to investigate the hypothesis in larger epidemiological samples and define a gold standard assessment protocol involving non-invasive sampling methods.

Physical activity could be a key element in the implementation of health promotion strategies.

5. In the meantime

The more traditional approach to investigate the working environments impact on workers health consists in the assesment of potential outcomes related to the exposure to harmful or potentially detrimental agents. Despite the laws in force (Legislative Decree No 81/2008) recommend the substitution of harmful agents and the minimisation of exposed workers, some activities still require their manipulation. The implementation of prevention strategies is thus fundamental to guarantee the health of the workers involved. Whereas for some agents the exposure is allowed under specific threshold limits, in other scenarios the working activity may involve the manipulation of agents whose potential effects are still not completely assessed or currently under investigation.

In both situations, the biomonitoring, i.e. the measurement of the concentration of chemicals, their metabolites or markers of subsequent health effects in human biological media (Angerer et al. 2011), assumes a pivotal role. The goal of human biomonitoring is three-fold: (i) the assessment of the exposure; (ii) the identification of early effects which could be considered as hallmarks of health effects; and (iii) the assessment of a health risk in exposed subjects (Bergamaschi et al. 2015).

Moreover, the harmful health effects can be different depending on the chemical agents, the time of exposure, and the individual susceptibility (Santovito et al. 2016).

5.1. Formaldehyde exposure and Health

Several studies, to date, have focused on hospital workers and their occupational risks (Santovito et al. 2016; da Silva, Giuntini, and Meneguin 1997; Santovito et al. 2011; Santovito, Cervella, and Delpero 2014; Ioannou et al. 2017), e.g., operating theatre nurses and pathologists, including those who are chronically exposed to formaldehyde (FA) (Ruberto and Santovito 2021; Bellisario et al. 2016; F. Ghelli, Cocchi, et al. 2021a). FA is a ubiquitous toxic highly reactive chemical with carcinogenic properties (Zhao et al. 2021; Kang et al. 2021) produced worldwide and employed in an extremely wide variety of industrial and medical processes (Costa et al. 2013).

THe inalation of FA has been associated with several toxic effects: low exposure levels (0.1 ppm) can irritate the eyes, nose and upper respiratory airways, while high concentrations may result in pulmonary function impairment and asthma (Rumchev et al. 2002; Yang et al. 2001). Prolonged exposure to FA has been also associated with nasopharyngeal cancer (Hauptmann et al. 2004; Beane Freeman et al. 2013) and leukaemia (Beane Freeman et al. 2013; Allegra et al. 2019), and there is limited evidence of a possible association of this compound with sinonasal cancer (Nielsen, Larsen, and Wolkoff 2017). In this context, the International Agency for Research on Cancer (IARC) classifies FA as "*carcinogenic to humans (Group 1)*" ("Formaldehyde, 2-Butoxyethanol and 1-Tert-Butoxypropan-2-Ol." 2006). Despite its harmful characteristics, FA is still widely used in pathology wards, where it has been used as fixative for almost 100 years due to its unique ability in preserving cell and tissue morphology (Shaham, Gurvich, and Kaufman 2002; Motta et al. 2021). Hence, the long-standing concerns over the adverse health effects related to FA exposure (L. Zhang et al. 2010) in this population. However, due to the current lack of an effective alternative chemical, the use of formalin is still needed, making it necessary to arrange various measures to control workers' exposure, such as the isolation of activities producing greater emissions and the adoption of new standard procedures in order to reduce the number of samples soaked into formalin (Fustinoni et al. 2021). The possible mechanisms underlying the FA-induced long-term effects include inflammation, oxidative stress (OS), and apoptosis (Seow et al. 2015).

The FA genotoxic effect, instead, is still debated. Cytogenetic outcomes, such as increased chromosomal aberrations (CAs) and micronucleated cells (MNc), were reported in some biomonitoring studies (Santovito et al. 2011; Souza and Devi 2014) on chronic exposures, while this evidence was lacking in other published reports (Pala et al. 2008; Peteffi et al. 2016). However, the genomic damage level due to occupational exposure to xenobiotics depends also on the individual susceptibility. From the genetic point of view, this is due to polymorphisms in a battery of genes, mainly involved in metabolic and DNA-repair pathways (Crocco et al. 2019). The heritable variability of these genes may be associated with an altered efficiency of the processes in which they are involved (Christiani, Mehta, and Yu 2008). Among these, the enzymes belonging to the glutathione S-transferase (GST) and cytochrome P450 (CYP) families take part in a two-step detoxification process of a wide spectrum of environmental xenobiotics (Parveen et al. 2009; Yang et al. 2001). Moreover, in order to safeguard the genome's integrity and to prevent the potentially mutagenic consequences of DNA modifications, the cells evolved several mechanisms of DNA repair, according to the type of damage. The Base Excision Repair (BER) and the Nucleotide Excision Repair (NER) correct DNA small base changes (oxidation or alkylation) and bulky adducts, pyrimidine dimers and inter-strand cross-links, respectively (Desaulniers et al. 2015). These DNA-repair genes, which are involved in the protection mechanism against cancer development, are polymorphic (Desaulniers et al. 2015). Several evidences reported that defects in these DNA repair mechanisms could reduce FA tolerance at cellular level (Viegas et al. 2010).

The aims of the three studies conducted on this topic were:

- The evaluation of the systemic oxidative and inflammatory status alteration in a hospital working population routinely exposed to air-FA. To better understand the role of inter-individual differences in the exposure-related outcomes, all participants were genotyped for polymorphisms involved in xenobiotic metabolism and in cytokine production, and specifically: *CYP1A1 exon 7 (A > G)*, which is involved in phase I metabolic pathways, *GSTT1* (Positive/null) and *GSTM1* (Positive/null), which are involved in phase II reactions, and, finally, *TNF-α (−308, G > A)* and *IL-6 (−174, G > C)* to evaluate the possible role of an alteration in the production of cytokines involved in long-term inflammation processes (Federica Ghelli, Bellisario, et al. 2021)
- The assessment of the frequency of human chromosomal aberrations (CAs – measured in Peripheral Blood Lymphocytes, PBLs) and the risk/protective role played by several genetic polymorphisms, in a cohort of 57 exposed pathologists and 48 controls. All subjects were genotyped for the most common cancer-associated gene polymorphisms which could be related with the genotoxic outcome: *CYP1A1* exon 7 (A > G), *CYP1A1*2A* (T > C), *CYP2C19*2* (G > A), *GSTT1* (Positive/Null), *GSTM1* (Positive/null), *GSTP1* (A > G), *XRCC1* (G399A), *XRCC1* (C194T), *XRCC1* (A280G), *XPD* (A751C), *XPC exon 15* (A939C), *XPC exon 9* (C499T), *TNFα − 308* (G > A), *IL10 − 1082* (G > A), *IL10 − 819* (C > T) and *IL6 − 174* (G > C)(F. Ghelli, Cocchi, et al. 2021b) .
- The evaluation of the frequency of sister-chromatid exchanges (SCEs) in cultured PBLs on the same population as above, and the risk/protective role played by the most common cancer-associated gene polymorphisms: *CYP1A1* exon 7 (A > G), *CYP1A1*2A* (T > C), *CYP2C19*2* (G > A), *GSTT1* (presence/absence), *GSTM1* (presence/absence), *GSTP1* (A > G), *XRCC1* (G399A), *XRCC1* (C194T), *XRCC1* (A280G), *XPC* exon 15 (A939C), *XPC* exon 9 (C499T), *TNFα* − 308 G > A), *IL10* – 1082 (G > A), and *IL6* − 174 (G > C) (Federica Ghelli, Cocchi, et al. 2022).

In the formalin-employers group we assessed significantly higher levels of 15-F2t-IsoP, MDA and TNFα (<0.001) in comparison to the non-employers group. The air-FA levels turned out to be positively correlated with 15-F2t-IsoP ($p = 0.027$) and MDA ($p < 0.001$). In the formalin-employers group the MDA level was significantly higher in GSTT1 Null ($p = 0.038$), GSTM1 Null ($p = 0.031$), and

CYP1A1 exon 7 mutation carrier (p = 0.008) workers, compared to the wild type subjects, as can be seen in **Figure 32** (Federica Ghelli, Bellisario, et al. 2021).

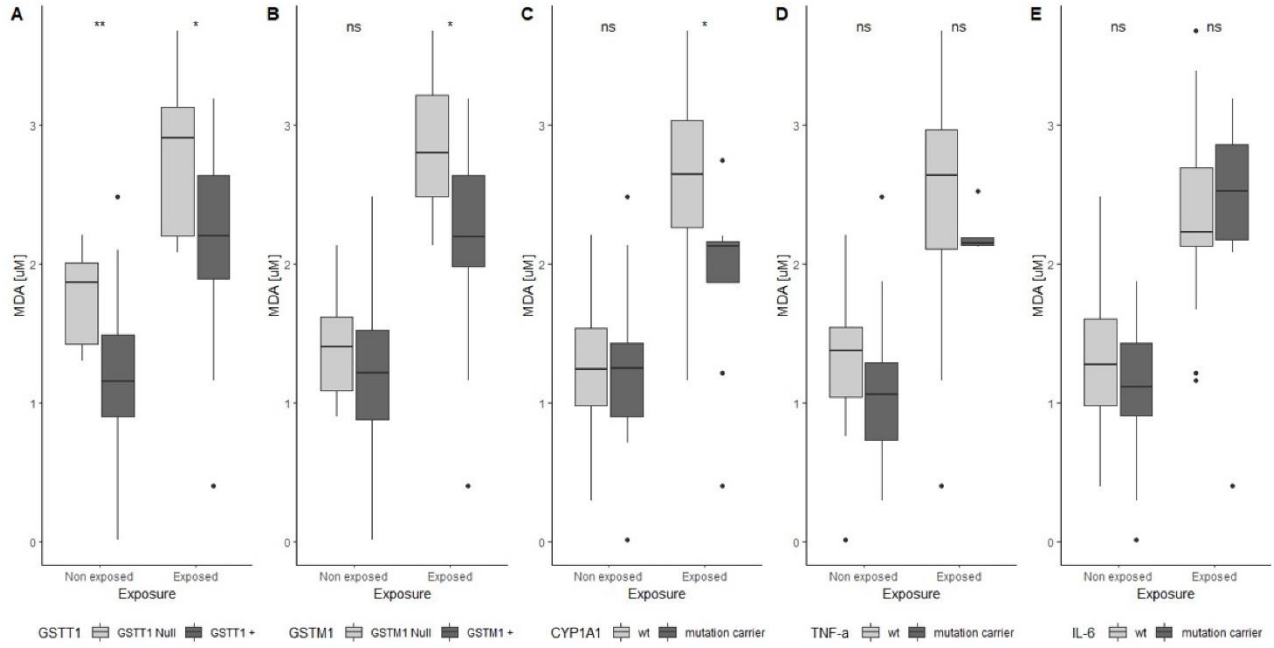


Figure 32: Boxplot of MDA levels in formalin-employers and non-employers according to the five polymorphisms analysed: (A) GSTT1, (B) GSTM1, (C) CYP1A1, (D) TNF-α, (E) IL-6. In each panel the non-employers data are depicted on the left side, while the formalin-employers data are on the right. In each group, the boxplot in light grey shows the mutation carriers for the selected genes, while the boxplot in dark grey is related to the wt. *: $p < 0.05$, **: $p < 0.01$, ns: not significant, dots represent the outliers.

The comparison between pathologists and controls showed a significantly higher CAs frequency in pathologists. Significant positive correlations were found between CAs frequency and air-FA concentration while significant associations were found between variation in CAs frequency and the mutated allele for *CYP1A1 exon 7 (A>G)*, *CYP2C19*2 (G>A)*, *GSTT1*-positive, *GSTM1*-positive and *XRCC1 (G399A)* (Federica Ghelli, Cocchi, et al. 2021). Pathologists, exposed to 55.2 µg/m3 of air-FA, showed a significantly higher SCEs frequency than controls, exposed, respectively, to 18.4 µg/m^3. Air-FA was directly correlated with SCEs frequency and inversely with the replication index (RI). Regression models showed FA exposure as a significant predictor in developing SCEs, while did not highlight any role of the selected polymorphisms (Federica Ghelli, Cocchi, et al. 2022).

The main limitation of these studies is the cross-sectional design, which prevents the possibility of causal inferences. Longitudinal studies should be performed, in order to clarify causes of oxidative and inflammatory status alteration. The strengths, on the other hand, consist in the quantification of personal exposure of workers enrolled in the study and in the measurement of many different biomarkers representing the different pathways that could be altered following the FA exposure. In addition, having also considered the genetic differences that could have an impact in the responsiveness to harmful exposure allowed us to highlight the importance of considering individual susceptibility in occupational settings (Federica Ghelli, Bellisario, et al. 2021).

In terms of public health and preventive strategies, gathering information on the different factors able to influence the biological outcome onset is of utmost importance in order to allow the definition of exposure limits or the safety of workers (Federica Ghelli, Bellisario, et al. 2021).

5.2. NanoExplore Project

The LIFE NanoEXPLORE project was a pilot study implemented in four European countries (Greece, Italy, Spain and the UK) started in 2018 to develop technologies and online tools to monitor the exposure to nanomaterials (NMs), implementing an integrated approach for exposure and health effects monitoring of nanocomposites in workplaces and urban areas. Alongside with the particles quantification and characterisation, the project implemented a bio-monitoring protocol to identify possible health effects eventually tributable to the NMs exposure, including the effects of inhalation. Indeed, the nanotechnology field is currently fast growing, due to its potential to develop new add-values products. The increase in production and availability of nanotechnology-based products result in a number of innovative applications, but can also be associated to human exposure, with the potential for unforeseen biological effects. Particularly, workers involved in manufacturing and handling nanomaterials are likely to have regular exposures to engineered nanomaterials and incidental ultrafine dusts.

Since the main exposure route is inhalation, the two biological matrices investigated were urine (to analyse the eventual early biological effects at systemic level) and Exhaled Breath condensate (EBC – to investigate the same effects at local level). The matrix choice was due to the non-invasive method required for the collection, making them the election choice to maximise the workers' compliance. Among non-invasive matrices, EBC is a validated method for assessing volatile markers and inflammatory mediators. This methodology allows collecting droplets from airway lining fluid by the condensation of warm, humid breath onto a cold surface in a condensing device (Federica Ghelli, Panizzolo, Garzaro, Squillacioti, Bellisario, Colombi, Bergamaschi, Guseva Canu, et al. 2022). The biomarkers investigated in EBC were 15-F2t-Isop, MDA, nitrotyrosine, High-Sensitivity C reactive protein (Hs-CRP), IL-1β, TNF-α, IL-10 and KL-6, whereas in urine the biomarkers assessed were 15-F2t-Isop, MDA, and TAP.

The study was design is an international multicenter prospective cohort. In both the recruitment and follow-up field campaigns, biological matrix (urine and EBC) sampling for biomarker analysis will be conducted twice, pre- and post-shift, respectively (**Figure 33**).

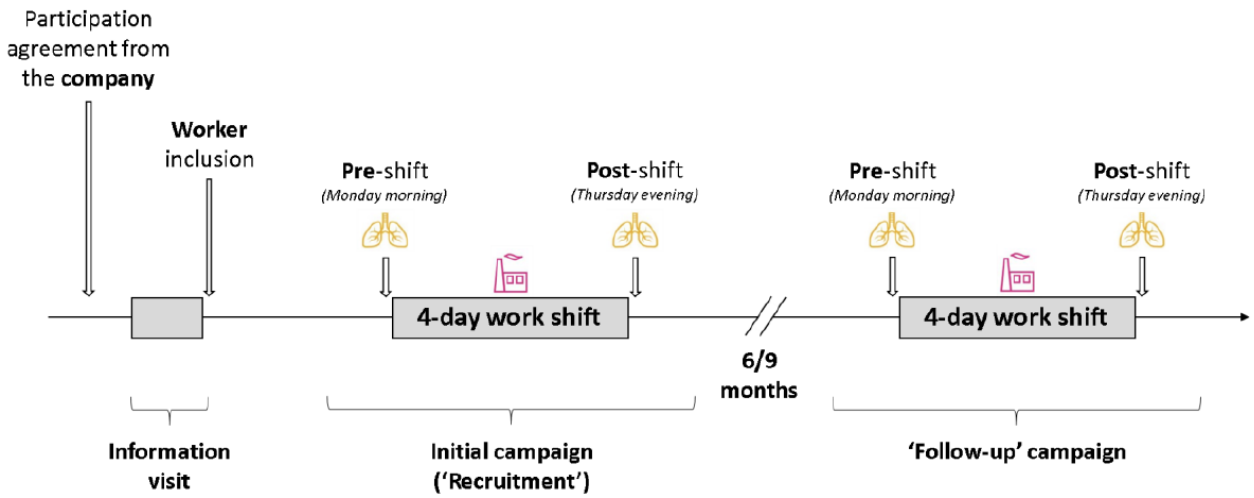


Figure 33: Pilot study design. External exposure (symbol: plant) will be monitored during a 4-day work shift. Biological matrices (i.e. EBC, EA and urine; symbol: lungs) for biomarker evaluations will be sampled in pre- and post-shift. An information visit conducted beforehand provided to collect company-related information, inform and enroll volunteer participants.

In the framework of this project, a systematic review was carried out to compare the baseline values of pro/anti-inflammatory biomarkers most commonly measured in EBC (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α, and CRP) in healthy, non-smoking adults, in order to provide a summary of the concentrations reported in the literature, as summarysed in **Figure 34**.

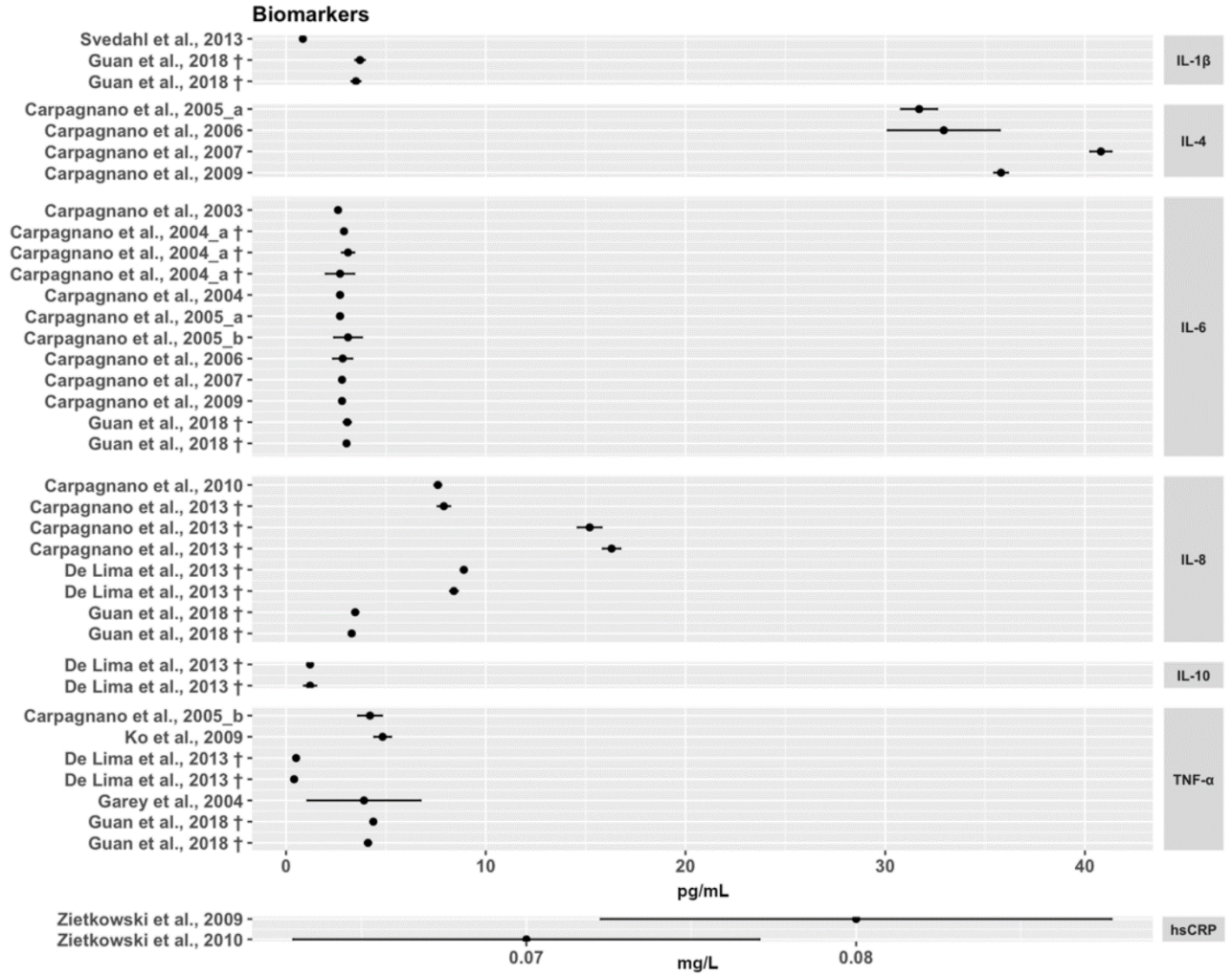


Figure 34: Forest plot summarising the concentration of the selected biomarkers in the articles where the sensitivity of the employed assays, and the measurements above the LOD were reported. † More subjects groups were analysed in the same article. The "a" and "b" following the indication of articles with the same first author and year are referred to the order of the articles in the bibliography paragraph (Z. Zietkowski et al. 2009; Carpagnano et al. 2003; Carpagnano, Kharitonov, et al. 2004; Carpagnano, Resta, et al. 2004; Carpagnano, Foschino Barbaro, et al. 2005; Carpagnano, Barbaro, et al. 2005; Carpagnano et al. 2006; 2007; 2010; 2013; de Lima et al. 2013; Carpaganano et al. 2009; Garey et al. 2004; Guan et al. 2018; Ko et al. 2009; Svedahl et al. 2013; Z. Zietkowski et al. 2010).

The analysis of the included articles, besides, highlighted wide differences in the methodologies employed in the included articles concerning EBC sampling, storage, and analyses, research protocols were assessed specifically to test their adherence to the ATS/ERS Task Force guidelines on EBC. These findings strengthen the importance to develop reference intervals for these biomarkers, which can result in their introduction and use in both research and clinical settings, not only for monitoring purposes but also, in the perspective of future longitudinal studies,

as predictive parameters for the onset and development of chronic diseases with inflammatory aetiology (Federica Ghelli, Panizzolo, Garzaro, Squillacioti, Bellisario, Colombi, Bergamaschi, Guseva Canu, et al. 2022).

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7. Appendices

7.1. Appendix A – Search Strings

Search strings employed in the article query.

PubMed

#1 "Oxidative Stress"[Mesh]
#2 oxidative[tiab] OR oxidation[tiab] OR oxidant[tiab] OR anti-oxidant[tiab] OR antioxidant[tiab] OR antioxidative[tiab] OR anti-oxidative[tiab]
#3 "Inflammation"[Mesh]
#4 inflammat*[tiab] OR pro-inflammat*[tiab] OR anti-inflammat*[tiab] OR antiinflammat*[tiab] OR antinflammat*[tiab]
#5 "Hydrocortisone"[Mesh]
#6 cortisol*[tiab] OR hydrocortison*[tiab]
#7 "Malondialdehyde"[Mesh]
#8 malondialdehyde[tiab] OR malonylaldehyde[tiab] OR malonaldehyde[tiab] OR malonyldialdehyde[tiab] OR MDA[tiab]
#9 "8-Hydroxy-2'-Deoxyguanosine"[Mesh]
#10 8-hydroxy-2'-deoxyguanosine[tiab] OR 8-hydroxy-deoxyguanosine[tiab] OR 8-hydroxydeoxyguanosine[tiab] OR 8-hydroxyguanine[tiab] OR 8-hydroxy-guanine[tiab] OR 8-Oxo-2'-Deoxyguanosine[tiab] OR 8-Oxo-Deoxyguanosine[tiab] OR 8-oxo-dGuo[tiab] OR 8-Ohdg[tiab] OR 8OHdG[tiab] OR 8-OH-dG[tiab] OR 8-ohg[tiab] OR 8-hydroxy-g[tiab] OR 8-hydroxy-dg[tiab] OR 8-oxodG[tiab] OR 8-oxodGuo[tiab] OR 8-oxo-dG[tiab] OR 8-OH-2dG*[tiab] OR 8-isoprostane*[tiab]
#11 "F2-Isoprostanes"[Mesh]
#12 IsoP[tiab] OR F2-isoprostane*[tiab]
#13 "Dinoprost"[Mesh]
#14 dinoprost[tiab] OR 15-f2t-isop[tiab] OR 8-iso-PGF2a[tiab] OR 8-isoprostaglandin-f2[tiab] OR 8-iso-prostaglandin-f2[tiab] OR 8-iso-PGF2a[tiab] OR 8-epi-prostaglandin-F2alpha[tiab] OR 8-epi-prostaglandin-f2alpha[tiab] OR 8-epiprostaglandin-f2alpha[tiab] OR 8-epi-PGF2alpha[tiab]
#15 "C-Reactive Protein"[Mesh]
#16 C-reactive-protein[tiab] OR CRP[tiab]
#17 "Interleukin-6"[Mesh]
#18 interleukin-6[tiab] OR IL6[tiab] OR IL-6[tiab]
#19 "Interleukin-8"[Mesh]
#20 interleukin-8[tiab] OR IL-8[tiab] OR IL8[tiab]
#21 "Interleukin-1"[Mesh]
#22 interleukin-1[tiab] OR IL1[tiab] OR IL-1[tiab]
#23 "Tumor Necrosis Factor-alpha"[Mesh]
#24 Tumor-Necrosis-Factor-alpha[tiab] OR Tumor-Necrosis-Factor-a[tiab] OR TNF-alpha[tiab] OR TNFalpha[tiab] OR TNF-a[tiab] OR TNFa[tiab] OR cachectin[tiab] OR cachexin[tiab]
#25 "Melatonin"[Mesh]
#26 melatonin*[tiab]
#27 "6-sulfatoxymelatonin"[Supplementary Concept]
#28 6-sulfatoxymelatonin*[tiab] OR 6-sulfatoxy-melatonin*[tiab] OR 6-sulphatoxymelatonin*[tiab] OR 6-sulphatoxy-melatonin*[tiab] OR 6-hydroxymelatonin*[tiab] OR 6-hydroxy-melatonin*[tiab]

#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 "Quality of Life"[Mesh]
#31 quality-of-life[tiab] OR life-quality[tiab] OR QoL[tiab] OR HRQoL[tiab] OR HR-QoL[tiab] OR WHOQOL-bref*[tiab] OR World-Health-Organization-Quality-of-Life[tiab]
#33 "healthy days"[tiab]
#34 #30 OR #31 OR #32
#35 "Work"[Mesh]
#36 "Employment"[Mesh]
#37 "Occupations"[Mesh]
#38 "Occupational Groups"[Mesh]
#38 "Job Satisfaction"[Mesh]
#39 "Occupational Stress"[Mesh]
#40 "Occupational Health"[Mesh]
#41 "Occupational Exposure"[Mesh]
#42 work*[tiab] OR job[tiab] OR jobs[tiab] OR occupation*[tiab] OR profession*[tiab] OR shift[tiab] OR shifts[tiab] OR employe*[tiab] OR personnel[tiab] OR staff*[tiab] OR manager*[tiab]
#43 workaholi*[tiab] OR work-addict*[tiab] OR burn-out[tiab] OR burnout[tiab] OR burned-out[tiab]
#44 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
#45 #29 AND #34 AND #44

Embase

#1 'oxidative stress'/exp
#2 oxidative:ti,ab,kw OR oxidation:ti,ab,kw OR oxidant:ti,ab,kw OR 'anti oxidant':ti,ab,kw OR antioxidant:ti,ab,kw OR antioxidative:ti,ab,kw OR 'anti oxidative':ti,ab,kw
#3 'inflammation'/de
#4 inflammat*:ti,ab,kw OR 'pro inflammat*':ti,ab,kw OR 'anti inflammat*':ti,ab,kw OR antiinflammat*:ti,ab,kw OR antinflammat*:ti,ab,kw
#5 'hydrocortisone'/exp
#6 cortisol*:ti,ab,kw OR hydrocortison*:ti,ab,kw
#7 'malonaldehyde'/exp
#8 malondialdehyde:ti,ab,kw OR malonylaldehyde:ti,ab,kw OR malonaldehyde:ti,ab,kw OR malonyldialdehyde:ti,ab,kw OR mda:ti,ab,kw
#9 '8 hydroxydeoxyguanosine'/exp
#10 '8 hydroxy 2 deoxyguanosine':ti,ab,kw OR '8 hydroxy deoxyguanosine':ti,ab,kw OR '8 hydroxydeoxyguanosine':ti,ab,kw OR '8 hydroxyguanine':ti,ab,kw OR '8 hydroxy guanine':ti,ab,kw OR '8 oxo 2 deoxyguanosine':ti,ab,kw OR '8 oxo deoxyguanosine':ti,ab,kw OR '8 oxo dguo':ti,ab,kw OR '8 ohdg':ti,ab,kw OR 8ohdg:ti,ab,kw OR '8 oh dg':ti,ab,kw OR '8 ohg':ti,ab,kw OR '8 hydroxy g':ti,ab,kw OR '8 hydroxy dg':ti,ab,kw OR '8 oxodg':ti,ab,kw OR '8 oxodguo':ti,ab,kw OR '8 oxo dg':ti,ab,kw OR '8 oh 2dg*':ti,ab,kw OR '8 isoprostane*':ti,ab,kw
#11 'isoprostane derivative'/exp
#12 isop:ti,ab,kw OR 'f2 isoprostane*':ti,ab,kw
#13 'prostaglandin F2 alpha'/exp
#14 dinoprost:ti,ab,kw OR '15 f2t isop':ti,ab,kw OR '8 isoprostaglandin f2':ti,ab,kw OR '8 iso prostaglandin f2':ti,ab,kw OR '8 iso pgf2a':ti,ab,kw OR '8 epi prostaglandin f2alpha':ti,ab,kw OR '8 epiprostaglandin f2alpha':ti,ab,kw OR '8 epi pgf2alpha':ti,ab,kw

#15 ‘c reactive protein’/exp
#16 ‘c reactive protein’:ti,ab,kw OR crp:ti,ab,kw
#17 ‘interleukin 6’/exp
#18 ‘interleukin 6’:ti,ab,kw OR il6:ti,ab,kw OR ‘il 6’:ti,ab,kw
#19 ‘interleukin 8’/exp
#20 ‘interleukin 8’:ti,ab,kw OR ‘il 8’:ti,ab,kw OR il8:ti,ab,kw
#21 ‘interleukin 1’/exp
#22 ‘interleukin 1alpha’/exp
#23 ‘interleukin 1beta’/exp
#24 ‘interleukin 1’:ti,ab,kw OR il1:ti,ab,kw OR ‘il 1’:ti,ab,kw
#25 ‘tumor necrosis factor’/exp
#26 ‘tumor necrosis factor-alpha’:ti,ab,kw OR ‘tumor necrosis factor-a’:ti,ab,kw OR ‘tnf-alpha’:ti,ab,kw OR tnfalpha:ti,ab,kw OR ‘tnf-a’:ti,ab,kw OR tnfa:ti,ab,kw OR cachectin:ti,ab,kw OR cachexin:ti,ab,kw
#27 ‘melatonin’/exp
#28 melatonin*:ti,ab,kw
#29 ‘6 hydroxymelatonin o sulfate’/exp
#30 ‘6 sulfatoxymelatonin*’:ti,ab,kw OR ‘6 sulfatoxy melatonin*’:ti,ab,kw OR ‘6 sulphatoxymelatonin*’:ti,ab,kw OR ‘6 sulphatoxy melatonin*’:ti,ab,kw OR ‘6 hydroxymelatonin*’:ti,ab,kw OR ‘6 hydroxy melatonin*’:ti,ab,kw
#31 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#32 ‘quality of life’/exp
#33 ‘quality of life’:ti,ab,kw OR ‘life quality’:ti,ab,kw OR QoL:ti,ab,kw OR hrQoL:ti,ab,kw OR ‘hr-QoL’:ti,ab,kw OR ‘whoQoL bref*’:ti,ab,kw OR ‘world health organization quality of life’:ti,ab,kw
#34 ‘healthy days’:ti,ab,kw
#35 #32 OR #33 OR #34
#36 ‘work’/exp
#37 ‘occupation’/exp
#38 ‘named groups by occupation’/exp
#39 ‘occupational health’/exp
#40 work*:ti,ab,kw OR job:ti,ab,kw OR jobs:ti,ab,kw OR occupation*:ti,ab,kw OR profession*:ti,ab,kw OR shift:ti,ab,kw OR shifts:ti,ab,kw OR employe*:ti,ab,kw OR personnel:ti,ab,kw OR staff*:ti,ab,kw OR manager*:ti,ab,kw
#41 workaholi*:ti,ab,kw OR ‘work addict*’:ti,ab,kw OR ‘burn out’:ti,ab,kw OR burnout:ti,ab,kw OR ‘burned out’:ti,ab,kw
#42 #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #31 AND #35 AND #42

Cochrane CENTRAL

#1 MeSH descriptor: [Oxidative Stress] explode all trees
#2 (oxidative OR oxidation OR oxidant OR anti-oxidant OR antioxidant OR antioxidative OR anti-oxidative):ti,ab,kw
#3 MeSH descriptor: [Inflammation] explode all trees
#4 (inflammat* OR pro-inflammat* OR anti-inflammat* OR antiinflammat* OR antinflammat*):ti,ab,kw
#5 MeSH descriptor: [Hydrocortisone] explode all trees

#6 (cortisol* OR hydrocortison*):ti,ab,kw
#7 MeSH descriptor: [Malondialdehyde] explode all trees
#8 (malondialdehyde OR malonylaldehyde OR malonaldehyde OR malonyldialdehyde OR MDA):ti,ab,kw
#9 MeSH descriptor: [8-Hydroxy-2'-Deoxyguanosine] explode all trees
#10 ("8-hydroxy-2'-deoxyguanosine" OR "8-hydroxy-deoxyguanosine" OR "8-hydroxydeoxyguanosine" OR "8-hydroxyguanine" OR "8-hydroxy-guanine" OR "8-Oxo-2'-Deoxyguanosine"):ti,ab,kw
#11 ("8-Oxo-Deoxyguanosine" OR "8-oxo-dGuo" OR "8-Ohdg" OR 8OHdG OR "8-OH-dG" OR "8-ohg" OR "8-hydroxy-g" OR "8-hydroxy-dg" OR "8-oxodG" OR "8-oxodGuo" OR "8-oxo-dG" OR "8-OH-2dG" OR "8-isoprostane"):ti,ab,kw
#12 MeSH descriptor: [F2-Isoprostanes] explode all trees
#13 (IsoP OR "F2-isoprostane"):ti,ab,kw
#14 MeSH descriptor: [Dinoprost] explode all trees
#15 (dinoprost OR "15-f2t-isop" OR "8-iso-PGF2a" OR "8-isoprostaglandin-f2" OR "8-iso-prostaglandin- f2" OR "8-iso-PGF2a" OR "8-epi-prostaglandin-F2alpha" OR "8-epi-prostaglandin-f2alpha" OR "8- epiprostaglandin-f2alpha" OR "8-epi-PGF2alpha"):ti,ab,kw
#16 MeSH descriptor: [C-Reactive Protein] explode all trees
#17 ("C-reactive protein" OR CRP):ti,ab,kw
#18 MeSH descriptor: [Interleukin-6] explode all trees
#19 (interleukin-6 OR IL6 OR IL-6):ti,ab,kw
#20 MeSH descriptor: [Interleukin-8] explode all trees
#21 (interleukin-8 OR IL-8 OR IL8):ti,ab,kw
#22 MeSH descriptor: [Interleukin-1] explode all trees
#23 (interleukin-1 OR IL1 OR IL-1):ti,ab,kw
#24 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees
#25 ("Tumor Necrosis Factor-alpha" OR "Tumor Necrosis Factor-a" OR TNF-alpha OR TNFalpha OR TNF-a OR TNFa OR cachectin OR cachexin):ti,ab,kw
#26 MeSH descriptor: [Melatonin] explode all trees
#27 (melatonin*):ti,ab,kw
#28 ("6-sulfatoxymelatonin" OR "6-sulfatoxy-melatonin" OR "6-sulphatoxymelatonin" OR "6-sulphatoxy-melatonin" OR "6-hydroxymelatonin" OR "6-hydroxy-melatonin"):ti,ab,kw
#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 MeSH descriptor: [Quality of Life] explode all trees
#31 ("quality of life" OR "life quality" OR QoL OR HRQoL OR HR-QoL OR WHOQOL-bref OR "World Health Organization Quality of Life" OR "healthy days"):ti,ab,kw
#32 #30 OR #31
#33 MeSH descriptor: [Work] explode all trees
#34 MeSH descriptor: [Employment] explode all trees
#35 MeSH descriptor: [Occupations] explode all trees
#36 MeSH descriptor: [Occupational Groups] explode all trees
#37 MeSH descriptor: [Job Satisfaction] explode all trees
#38 MeSH descriptor: [Occupational Stress] explode all trees
#39 MeSH descriptor: [Occupational Health] explode all trees
#40 MeSH descriptor: [Occupational Exposure] explode all trees

#41 (work* OR job OR jobs OR occupation* OR profession* OR shift OR shifts OR employe* OR personnel OR staff* OR manager* OR workaholi* OR work-addict* OR burn-out OR burnout OR burned-out):ti,ab,kw
#42 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #29 AND #32 AND #42

7.2. Appendix B – List of Publications

List of contribution already published

1. Squillacioti G, Bellisario V, Grosso A, **Ghelli F**, Piccioni P, Grignani E, Corsico A, Bono R. Formaldehyde, Oxidative Stress, and FeNO in Traffic Police Officers Working in Two Cities of Northern Italy. Int J Environ Res Public Health. 2020 Mar 4;17(5):1655. doi: 10.3390/ijerph17051655. PMID: 32143339; PMCID: PMC7084911.
2. **Ghelli F**, Bellisario V, Squillacioti G, Grignani E, Garzaro G, Buglisi M, Bergamaschi E, Bono R. Oxidative stress induction in woodworkers occupationally exposed to wood dust and formaldehyde. J Occup Med Toxicol. 2021 Feb 9;16(1):4. doi: 10.1186/s12995-021-00293-4. PMID: 33563312; PMCID: PMC7871551.
3. **Ghelli F**, Cocchi E, Buglisi M, Squillacioti G, Bellisario V, Bono R, Santovito A. The role of phase I, phase II, and DNA-repair gene polymorphisms in the damage induced by formaldehyde in pathologists. Sci Rep. 2021 May 18;11(1):10507. doi: 10.1038/s41598-021-89833-w. PMID: 34006906; PMCID: PMC8131755.
4. **Ghelli, F**.; Bellisario, V.; Squillacioti, G.; Panizzolo, M.; Santovito, A.; Bono, R. Formaldehyde in Hospitals Induces Oxidative Stress: The Role of *GSTT1* and *GSTM1* Polymorphisms. *Toxics* 2021, *9*, 178. https://doi.org/10.3390/toxics9080178
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10. Bono, R., Squillacioti, G., **Ghelli, F.**, Panizzolo, M., Comoretto, R. I., Dalmasso, P., & Bellisario, V. (2023). Oxidative Stress Trajectories during Lifespan: The Possible Mediation Role of Hormones in Redox Imbalance and Aging. *Sustainability*, *15*(3), 1814. https://doi.org/10.3390/su15031814

List of contribution under review or accepted

1. Physical Activity Working from Home During COVID-19 Pandemic: An Agreeable Way to Counteract the Oxidative Stress Burden - **F. Ghelli**, G. Squillacioti, V. Bellisario, S. El Sherbiny, F. Guglieri, G. M. Picone, U. Bena, R. Bono
2. Oxidative stress in the early neonatal period as a possible effect of BMI, smoking habits, and level of urbanization of the mother **-** E. Cocchi, G. Squillacioti, **F. Ghelli**, C. Plazzotta, T. Musso, L. Marozio, R. Bono, V. Bellisario

7.3. Appendix C – List of contributions to congresses

25/08/2019 – 28/08/2019 – Utrecht, The Netherlands

31st Annual Conference of the International Society for Environmental Epidemiology

- **Oxidative stress induction in woodworkers exposed to wood dust and formaldehyde**
  F, Ghelli; G, Squillacioti; V, Bellisario; R, Bono
  Environmental Epidemiology: October 2019 - Volume 3 - Issue - p 35
  doi: 10.1097/01.EE9.0000606012.89057.c0
- **Greenness effect on oxidative stress and respiratory flows in children**
  G, Squillacioti; V, Bellisario; F, Ghelli; P, Piccioni; E, Borgogno Mondino; R, Bono
  Environmental Epidemiology: October 2019 - Volume 3 - Issue - p 35-36
  doi: 10.1097/01.EE9.0000606016.27176.f4
- **Oxidative Stress Profile of workers exposed to formaldehyde in the hospital**
  V, Bellisario1; G, Squillacioti1; F, Ghelli1; R, Bono1
  Environmental Epidemiology: October 2019 - Volume 3 - Issue - p 35
  doi: 10.1097/01.EE9.0000606008.81434.75

12/10/2020 – 16/10/2020 – Roma

16th World Congress on Public Health 2020

- **Formaldehyde in hospitals can still represent a risk factor. Oxidative stress and GSTT1 polymorphism**
  F Ghelli, M Buglisi, V Bellisario, A Santovito, R Bono
  European Journal of Public Health, Volume 30, Issue Supplement_5, September 2020,ckaa166.340,
  https://doi.org/10.1093/eurpub/ckaa166.340
- **Cytogenetic effects among workers exposed to formaldehyde. The possible role of some polymorphisms**
  F Ghelli, V Bellisario, M Buglisi, E Cocchi, R Bono, A Santovito
  European Journal of Public Health, Volume 30, Issue Supplement_5, September 2020, ckaa166.346,
  https://doi.org/10.1093/eurpub/ckaa166.346

20/04/2021 – 22/04/2021 – Virtual Conference

10th International Conference on Nanotoxicology

- **A biomonitoring pilot study in workers exposed to pigmentgrade titanium dioxide (TiO2) during paints production**
  Bergamaschi E, Buglisi M, Bellisario V, Garzaro G, Caniglia M, Castrignanò G, Squillacioti G, Ghelli F, Mariella G, Carraro E, Bonetta S, Fenoglio I, Riganti C

23/08/2021 – 26/08/2021 – New York City (virtual)

33rd Annual Conference of the International Society for Environmental Epidemiology

- **15-F2t-Isoprostane during the lifespan: from children to middle age**
  Valeria Bellisario, Federica Ghelli, Giulia Squillacioti, Roberto Bono, Paola Dalmasso

- **Oxidative stress and inflammation on neonatal outcomes. The role of smoke, traffic exposure and BMI**
  Valeria Bellisario, Enrico Cocchi, Giulia Squillacioti, Federica Ghelli, Claudio Plazzotta, Roberto Bono
- **Asthma-like symptoms and oxidative stress in adults from the GEIRD Cohort**
  Giulia Squillacioti, Valeria Bellisario, Federica Ghelli, Pavilio Piccioni, Giuseppe Verlato, Roberto Bono

10/11/2021 – 12/11/2021 – Virtual Conference

14th European Public Health Conference.

- **Occupational exposure to formaldehyde and oxidative stress in Italian workers**
  G Squillacioti, V Bellisario, F Ghelli, R Bono

06/02/2022 – 10/02/2022 – Virtual Conference

33rd International Congress on Occupational Health 2022 (ICOH 2022)

- **Implementation of a harmonized approach for monitoring exposure to engineered and incidental nanoparticles and their potential health effects: First results from the EU-LIFE project NanoExplore**
  Irina Guseva Canu, Guillaume Suarez, Jean-Jacques Sauvain, Nancy B. Hopf, Camille Crézé, Maud Hemmendinger, Carlos Fito, Giulia Squillacioti, Federica Ghelli, Martina Buglisi, Giacomo Garzaro and Enrico Bergamaschi

22/06/2022 – 24/06/2022 – Parigi (FR)

24th International Conference on Oxidative Stress Reduction, Redox Homeostasis & Antioxidants

- **Physical activity at work: an agreeable way to counteract the oxidative stress burden**
  Ghelli Federica, Bellisario Valeria, Squillacioti Giulia, Panizzolo Marco, Bono Roberto
  (Oral presentation)

05/07/2022 – 08/07/2022 – Thessaloniki (GR)

19th International Conference on Nanosciences & Nanotechnologies (NN22)

- **Urinary excretion of metals in workers producing technological paints and coatings**
  M. Panizzolo, F. Ghelli, V. Bellisario, G. Squillacioti, G. Mariella, I. Guseva-Canu, C. Fito López, R. Bono, E. Bergamaschi (Oral presentation)

- **Biomarkers of oxidative stress in workers exposed to NMs**
  F. Ghelli, M. Panizzolo, G. Squillacioti, V. Bellisario, I. Guseva-Canu, R.Bono, E. Bergamaschi (Oral presentation)

18/09/2022 – 21/09/2022 – Atene - Virtual Conference

34th Annual Conference of the International Society for Environmental Epidemiology

- **Oxidative stress in workers in indoor and outdoor environments**
  M. Panizzolo, F. Ghelli, G. Squillacioti, E. Bergamaschi, R. Bono, V. Bellisario

28/09/2022 – 01/10/2022 – Padova

55° Congresso Nazionale SItI 2022

- **Biomarcatori di stress ossidativo ed escrezione urinaria di metalli in lavoratori professionalmente esposti a nanomateriali**
  F. Ghelli, M. Panizzolo, G. Squillacioti, V. Bellisario, G. Garzaro, G. Mariella, E. Bergamaschi, R. Bono
- **The features of the built environment to improve respiratory health and lifestyles in children**
  G. Squillacioti, S. De Petris, F. Ghelli, M. Panizzolo, S. Levra, E.C. Borgogno Mondino, R. Bono

09/11/2022 – 12/11/2022 – Berlino

15th European Public Health Conference 2022

- **Working re-organisation due to the pandemic may negatively affect workers' quality of life**
  F. Ghelli, V. Bellisario, G. Squillacioti, M. Panizzolo, R. Bono

7.4. Appendix D – List of pubblications *in extenso*