Environment International 178 (2023) 108048

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Chrono-modulated effects of external stressors on oxidative stress and damage in humans: A scoping review on night shift work

Konstantinos C. Makris [a,*], Behzad Heibati [a,b], Shan Zienolddiny Narui [c]

[a] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus
[b] Department of Research, Cancer Registry Norway, Oslo, Norway
[c] National Institute of Occupational Health, Oslo, Norway

ARTICLE INFO

Handling Editor: Marti Nadal

Keywords:
Oxidative stress
Personalized medicine
Personalized prevention
Precision medicine
Diurnal
Critical life stage
Circadian disruption
Chronobiology
Shift work

ABSTRACT

Background: Oxidative stress and tissue damage (OSD) play a pivotal role as an early-stage process in chronic disease pathogenesis. However, there has been little research to better understand the temporal (χρόνος[chronos]) dimensions of OSD process associated with environmental (non-genetic, including behaviors/lifestyle) and/or occupational stressors, like night shift work. OSD processes have recently attracted attention in relation to time-resolved external stressor trajectories in personalized medicine (prevention) initiatives, as they seem to interact with circadian clock systems towards the improved delineation of the early stages of (chronic) disease process.

Objectives: This work critically reviewed human studies targeting the temporal dynamics of OSD and circadian clock system's activity in response to environmental/occupational stressors; the case of night shift work was examined.

Methods: Being a key stressor influencing OSD processes and circadian rhythm, night shift work was evaluated as part of a scoping review of research in OSD, including inflammatory and metabolic processes to determine the extent of OSD research undertaken in human populations, methodologies, tools and biomarkers used and the extent that the temporal dimensions of exposure and biological effect(s) were accounted for. Online databases were searched for papers published from 2000 onwards, resulting in the selection of 53 original publications.

Results and discussion: The majority of studies (n = 41) took place in occupational settings, while the rest were conducted in the general population or patient groups. Most occupational studies targeted outcomes of oxidative stress/damage (n = 19), followed by the combination of OSD with inflammatory response (n = 10), and studies focused on metabolic outcomes (n = 12). Only a minor fraction of the studies measured biomarkers related to circadian rhythm, such as, melatonin, its metabolite, or cortisol. Night shift work was associated with select biomarkers of OSD and inflammation, albeit with mixed results. Although much progress in delineating the biological mechanisms of OSD process has been made, an equally thorough investigation on the temporal trajectory of OSD processes as triggered by environmental/occupational stressors in human studies has yet to fully evolve.

1. Introduction

The influence of *χρόνος* (chronos, time *in Greek*) dimensions in dictating the recurrence of typical lifestyle and behavioral habits and their interfacial connection with endogenous circadian or biological clock systems is of fundamental importance in disease pathogenesis.

Abbreviations: 4-HNE, 4-hydroxynonenal; aMT6s, 6-sulfatoxymelatonin; 8-Oh-dG, 8-Hydroxyguanosine; 8-oxoGua, 8-Oxoguanine; OGG1, 8-oxoguanine DNA glycosylase; Bmal1, Brain muscle ARNT-like1; ESS, Ergonomic shift work system; ESR, Erythrocyte sedimentation rate; f-NSW, Former-night shift workers; GSH/GSSG, Glutathione/glutathione disulfide; HHcy, Hyperhomocysteinaemia; MDA, Malondialdehyde; YYIRT, Mean yo-yo intermittent recovery test; NSW, Night shift workers; OSD, Oxidative stress and tissue damage; RRSYA, Ratio of rotating night shift years to age; r-NSW, Rotating-night shift workers; SGPT, Serum glutamic pyruvic transaminase; ox-LDL, Serum oxidized LDL; SOD, Superoxide dismutase; SOD2, Superoxide dismutase 2; TXN, Thioredoxin-1; tPA, Tissue-type plasminogen activator; TRAP, Total antioxidant potential.

* Corresponding author.
E-mail address: konstantinos.makris@cut.ac.cy (K.C. Makris).

https://doi.org/10.1016/j.envint.2023.108048
Received 14 February 2023; Received in revised form 13 June 2023; Accepted 15 June 2023
Available online 20 June 2023

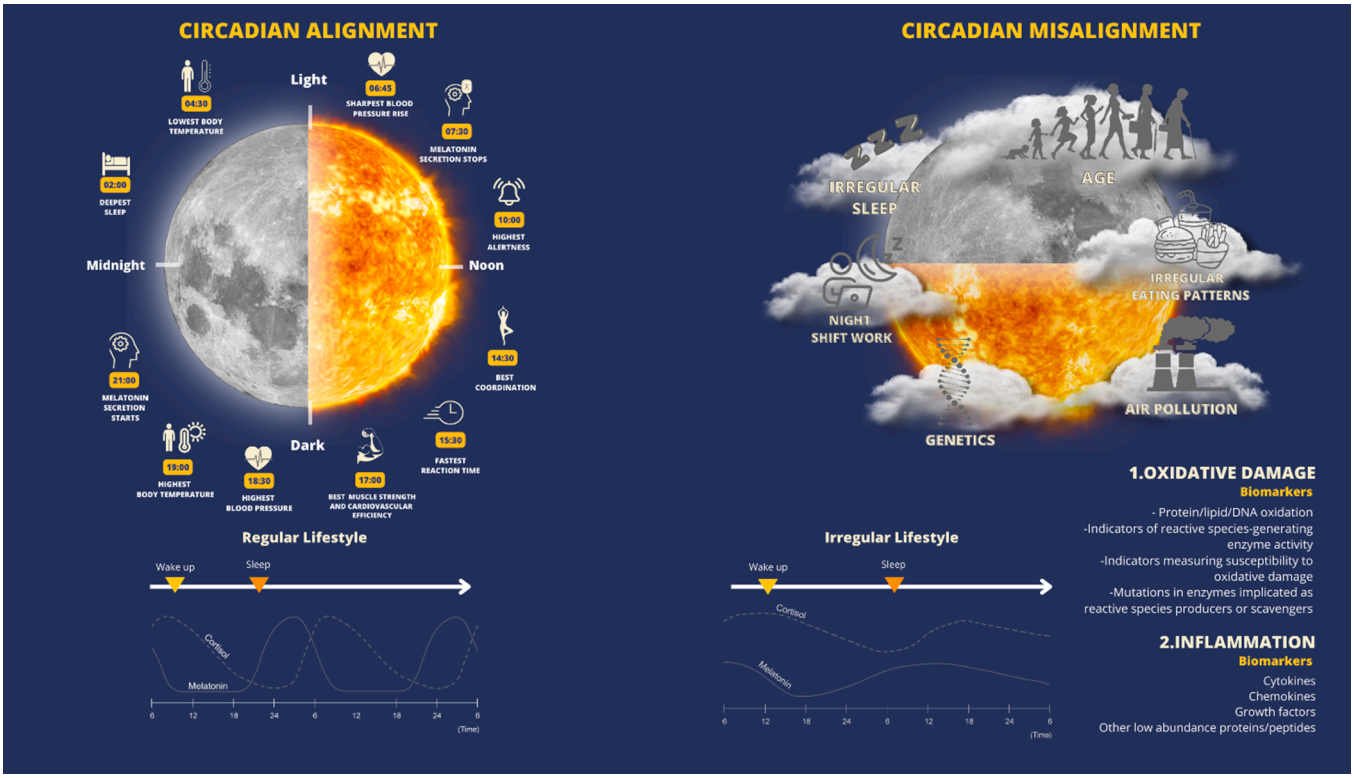

Fig. 1. Schematic showing the eurhythmic function of circadian clock system (left) and the set of risk factors associated with circadian misalignment (disruption) that often lead to downstream oxidative stress and damage including inflammation (right). The most important types of biomarkers of effect, such as oxidative damage and inflammation are also generally mentioned (bottom right). The eurhythmic function of circadian clock with well synchronized behaviors/lifestyle patterns are key in resilience and good health status, while desynchronized behaviors/lifestyle choices (e.g., irregular eating times, night shift work, irregular sleep) temporally shifting away from the dynamics of the circadian clock system(s) would potentially lead to adverse health and chronotoxicity outcomes.

However, there is little evidence from human studies on the temporal trajectory characteristics of the disease process. Time is invaluable in industrialized societies, where about half of the population may have disrupted circadian rhythms due to their daily schedule during working days (Dallmann et al. 2016b; Phillips 2009). These people are under the influence of the so-called social jet lag, which is the common phenomenon when an individual's internal and external cycles are not synchronized (Baron and Reid 2014; Roenneberg et al. 2007). Jet lag and negative effects of shift work represent examples of circadian-related disruptions. The temporal profiling of early-stage biological processes (e.g., oxidative stress/damage and inflammation) as part of the overall disease pathogenesis continuum has only recently received some attention, and they are worth of exploring further (Arora et al. 2021; Dallmann et al. 2016b; Phillips 2009). The dimensions of *χρόνος* are often under the influence of a dynamic equilibrium brought about by interfacial interactions between transient and temporally dynamic input systems that often prevail in biological systems.

The circadian misalignment and potential circadian disruption are a phenomenon of our time affecting millions of people around the globe (Fig. 1) (Crouse et al. 2021). Circadian rhythmicity and oxygen interactions in biological systems are of fundamental importance in disease pathogenesis (Sahar and Sassone-Corsi 2012a), and the same holds true for the circadian innate immunity and adaptive immune response (Wang et al. 2022). An earlier review focused on several diseases that exhibit strong linkages with oxidative stress and circadian rhythm processes, including aging, cardiovascular diseases, cancer, metabolic syndrome, and neurodegenerative disorders (Sahar and Sassone-Corsi 2012a). This critical review poses a personalized medicine/prevention-centered view of the χρόνος-modulating influence of circadian or diurnal systems on the early-stage linkages between environmental stressors and redox biology. Environmental stressors, such as diet, chemicals, light, sleep and work patterns span all types of non-genetic risk factors of human disease and they may be implicated with early-stage biological responses, such as those of oxidative stress and damage processes. Oxidative stress was defined as the disturbance in the prooxidant-antioxidant balance in favor of the former (Sies 1986). An updated definition was later formulated as the imbalance between oxidants and anti-oxidants in favor of the oxidants, leading to a disruption of redox signaling and induction of oxidative burst (Jones and Sies 2007). Most scientific evidence on the association between environmental/occupational insults and oxidative stress refer to animal models or *in-vitro* studies, while human studies usually represent a smaller fraction of the published literature. This knowledge gap hinders the better understanding of redox imbalance phenomena imposed by recurrent and time-varying exposures to environmental or occupational stressors. These stressors and the associated biological response appear in close connection with circadian misalignment and the documented mismatch between external and internal time.

This review is focused on human studies that target on the interfacial features between temporal dimensions of oxidative stress and tissue damage (OSD) and the temporal dynamics of circadian and other biological clock systems' activity as a result of environmental/occupational stressor exposures. Special focus was paid on night shift work as a key external stressor impacting circadian rhythmicity and resilience, while being potentially associated with OSD processes. As part of this work, a scoping review was conducted to systematically map the research done in the area of night shift work effects on OSD and inflammation and to identify knowledge gaps in the temporal dimensions of redox imbalance pathogenesis associated with the night shift work patterns. Such short (er)-term end points of disease process (e.g., oxidative stress, oxidative damage, or inflammation) may be better understood by focusing on the interfacial interactions between biological clock systems and processes

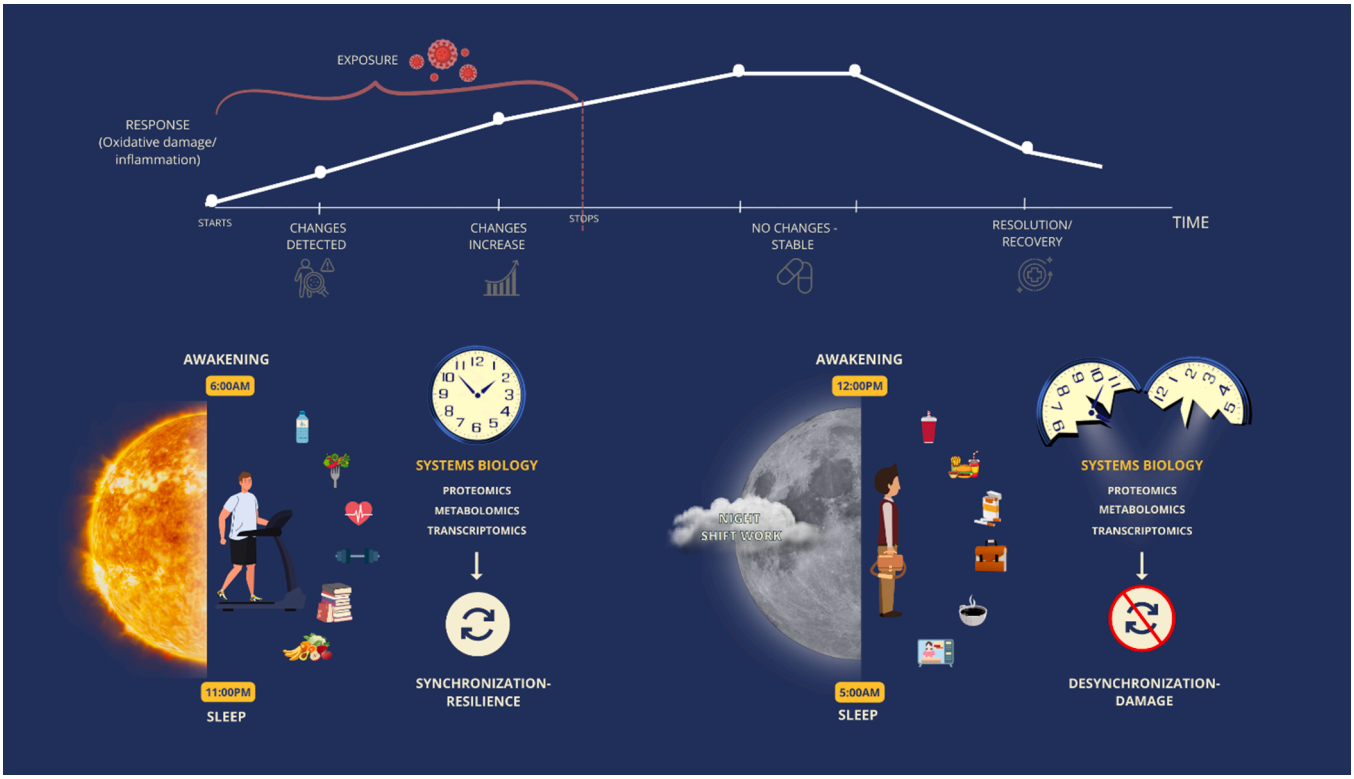

Fig. 2. Illustrative schematic of a reversible and proportional oxidative stress/damage disease process model, including its resolution (top) upon onset and end of exposure to an environmental stressor. Below, the essence of night shift work's chronotoxicity effects on oxidative stress/damage and/or inflammation is depicted, by demonstrating the importance of studying the desynchronized circadian clock regime. Desynchronized circadian clock system(s) might be the result of external stressors, e.g., systematic night shift work schedules that together with important confounders (diet, sleep, physical activity, light) would adversely impact endogenous response and disease process. This may be particularly well studied via a systems biology approach where various -omics platforms are utilized as intermediary biological layers of information between the exposures/stressors and the health outcomes under study.

(e.g., xenobiotic-metabolizing hepatic enzyme activity) and those of external environmental stressor time-activity-based exposures often leading to a differentiated disease phenotypic and cellular responses and repair patterns (Phillips, 2009). It is often the case that OSD and inflammatory processes, including their resolution stage, may occur interchangeably. Such literature studying both of these biological processes has been also considered here.

2. Fundamental characteristics of oxidative stress/damage

Reduction-oxidation ("redox") reactions represent a key mechanism of life that entails electron transfer from a donor ("reducing agent") to an acceptor ("oxidizing agent"). In 1985, the concept of oxidative stress was introduced for research in redox biology and medicine in the book entitled 'Oxidative Stress' (Sies 1986). Key mediators in the redox signaling and oxidative burst are low molecular mass reactive species derived from oxygen, nitrogen, iron in Fenton, and sulfur acting as redox signal factors at physiologically relevant concentrations. As such, low levels of reactive species (e.g., reactive oxygen species, ROS) contribute to the physiological homeostasis (redox signaling, "oxidative eustress") and they may become harmful at higher concentrations ("oxidative distress") (Sies 2017, 2020). In order to avoid accumulation of harmful ROS and oxidative distress, cells have evolved cellular antioxidant mechanisms, which are either enzymes themselves or non-enzymatic molecules that undergo oxidation (Kurutas 2015). ROS production by the phagocytes was first referred as the 'respiratory burst' or 'oxidative burst' due to the rapid and cyanide-insensitive increase in oxygen uptake, increase in glucose consumption, and immediate ROS release (El-Benna et al. 2016). A steady state redox balance is warranted to maintain homeostasis, while any deviation from the redox balance is viewed as a stress (Sies 2020). Free radical and non-radical oxidants exist in biological systems, while both may be implicated with oxidative stress. Superoxide radicals, peroxides, and hydroxyl radicals are common byproducts of cellular metabolism, acting as signaling molecules under physiological conditions. Also, non-radical oxidants, such as H_2O_2, reactive sulfur species, and metabolites with quinone and carbonyl structures contribute to OSD process. These reactive species may be counteracted by the production of protective enzymes that neutralize them, such as glutathione peroxidases, catalases, or superoxide dismutases, including small molecule antioxidants, such as vitamin E, C and A, uric acid and glutathione. These checks and balances may go beyond redox balance, causing cellular stress upon exposure to environmental cues (Ali et al. 2020).

In addition, OSD and inflammation processes are considered as key characteristics of human carcinogens (chemicals, physical or biological agents) (Guyton et al. 2018) by: i) being genotoxic, causing damage to DNA, such as DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis, intercalation, gene mutations, or cytogenetic changes (e.g. chromosome aberrations, micronuclei); ii) inducing oxidative stress, by producing oxygen radicals, and by inducing oxidative damage to macromolecules (e.g. DNA, proteins, lipids); iii) inducing chronic inflammation, such as elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production, and iv) being immunosuppressive by exhibiting decreased immunosurveillance and/or immune system dysfunction.

Inflammation includes injury, repair and resolution stages, where inflammatory cells (neutrophils, monocytes, macrophages, eosinophils, dendritic cells, mast cells and lymphocytes) are often recruited after an (oxidative) damage or an infection. The immune system is plastic, i.e., it has an unstable equilibrium representing a defense mechanism but also

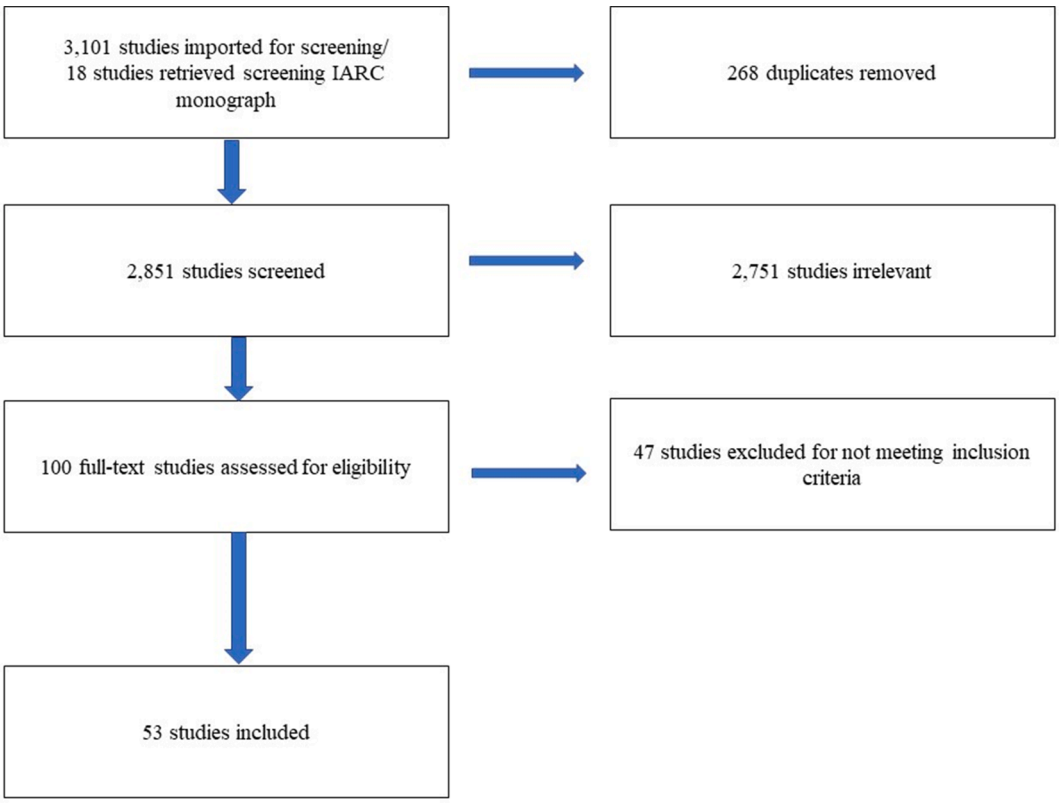

Fig. 3. Flowchart of article selection process in the scoping review that was centered around the night shift work effects on OSD processes.

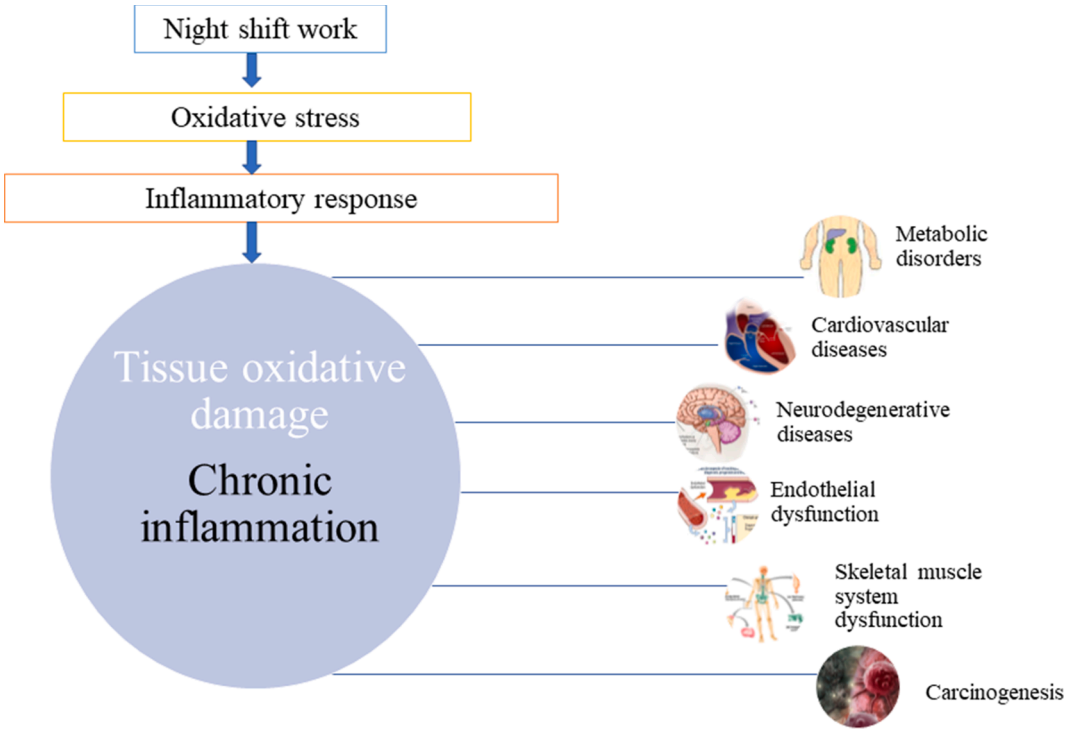

Fig. 4. The main chronic diseases associated with the onset and development of tissue oxidative stress/damage and inflammation processes under the influence of night shift work.

prone to causing impairment and disease (McEwen and Stellar 1993). Inflammation is also considered a key characteristic of the ageing process via ROS-mediated exacerbation of telomere dysfunction and cell senescence, and in the absence of any other genetic or environmental factors, researchers have coined the term of "inflammageing" (Franceschi et al. 2018). Systemic chronic inflammation triggered by social and

environmental factors (Berger et al. 2019) is a critical etiological element of a suite of non-communicable diseases associated with older age, including cardiovascular diseases, metabolic diseases, hormonal type of cancers, neurodegenerative disorders, among others (Prescott 2013) (Fig. 4). As an example, obesity is well tied to inflammation with evidence suggesting that adipose tissue may be associated with higher levels of inflammatory markers, such as, TNFa, IL-6, IL-1β (Gregor and Hotamisligil 2011).

3. Biomarkers of oxidative stress and damage in human studies

The reactive species associated with oxidative stress and/or damage are typically characterized by very short half-lives, making difficult to measure them in biospecimen collected as part of epidemiological or toxicological studies. Thus, the biomarkers of oxidative stress are often the products of the oxidation of cellular molecules by ROS in blood, urine or exhaled breath, depending on the biomarker of interest. Various biomarkers of oxidative stress with clinical or research relevance have been used in studies involving cardiovascular outcomes, metabolic, mental health, respiratory, or autoimmune diseases. These biomarkers include, but not limited to, xanthine oxidase, Nrf2, protein carbonyls, 3-nitrotyrosine, 3-chromotyrosine, protein thiol/disulfide, protein glutathionylation, GSH/GSSG, cysteine/cystine, oxidized low density lipoprotein (oxLDL), 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), F2-isoprostane, 8-OhdG, asymmetric dimethylarginine, nitrogen species, such as peroxynitrite (ONOO) and nitrogen dioxide (NO_2), and advanced glycation end products (Frijhoff et al. 2015). These molecules are broadly classified into three categories: lipid, protein, and nucleic acid (DNA) oxidation products, and they also include molecules, like GSH, which levels decrease as a result of oxidative stress. It has been argued that the above-mentioned biomarkers measure the magnitude of oxidative damage rather than that of the oxidative stress (Ghezzi 2020). Under oxidative stress conditions, the most abundant lipid-derived oxidation product is 4-HNE, which at low levels, it promotes cell proliferation while at higher concentrations, it induces oxidative DNA alterations and cell apoptosis (Federico et al. 2007). A second type of biomarkers are indicators of ROS-generating enzyme activity, such as uric acid and allantoin, or stable products of ROS-generating xanthine oxidase (XO) (Ghezzi 2020). A third type of biomarkers measures factors that assess susceptibility to oxidative damage, such as enzymes (superoxide dismutase, SOD, or catalase, CAT) and small-molecular weight molecules (e.g., vitamins C and E, bilirubin) that react with ROS and are often generically described as antioxidants or scavengers; this group also includes enzymes that produce ROS (e.g., NADPH oxidases (NOX), and XO). A fourth type of biomarkers of oxidative stress measure genetic variations known as polymorphisms in various metabolizing, detoxification, conjugation and repair enzymes implicated in ROS production or elimination. These markers provide information on host genetic factors determining the susceptibility to environmental stressors, and thus indicate a role for intrinsic host defense factors modulating oxidative stress in a specific disease process. In the case of inflammatory response, a suite of soluble and circulating cytokines, chemokines, growth factors (CCGFs) and other low abundance proteins/peptides in plasma, urine or saliva have been historically used to measure host inflammatory response to environmental stressors (Khan 2012) (Fig. 1).

The above-mentioned biomarkers of oxidative stress/damage and inflammation have been extensively used in human studies to evaluate associations with a suite of environmental stressors. They have been also used to estimate the associated mortality and morbidity burden of disease (the reader may consult excellent works by van't Erve et al., 2017; Linet et al., 2015).

4. Links between oxidative stress and inflammation in human studies

The difficulty of disentangling oxidative stress from inflammatory processes in biological systems is well noted in the literature. Chronic inflammation is capable of inducing an oxidative/nitrosative stress status characterized by DNA damage and genomic instability via a well-controlled feedback loop (Federico et al. 2007). Broadly, tissue injury progression as a result of environmental insults (e.g., dust, chemicals, light at night, diet, sleep loss) has been explained on the basis of three inter-connected mechanisms: i) inflammatory cell response, ii) production of reactive species/free radicals that damage cell membranes causing lipid peroxidation contributing to injury progression, and iii) leakage of degradative enzymes or "death proteins" from dying/injured cells (Mehendale 2005). DNA/protein/lipid damage as a result of external insults may signal an inflammatory response to the damaged area either by extending the damage or by rebuilding tissue architecture with cell proliferation from nearby healthy cells. It is often the case that an inflammatory response is accompanied by oxidative stress via the release of free radicals from leukocytes, including activated macrophages, which may damage the neighboring cells (Hussain et al. 2003). Additionally, misrepair and excessive cell proliferation can cause chronic irreversible effects, including carcinogenesis (Klaunig and Wang 2018). Similar biological processes have been observed in studies investigating the effects of ozone gas exposure on epithelial cell membrane oxidation, which triggers the release of inflammatory cells and stimulates irritant receptors in airway cell walls (Smith and Kriebel 2010).

Oxidative stress is implicated in the pathophysiology of several disease outcomes, including cardiovascular disease (Harrison et al. 2003) and so does inflammation (Libby 2006; Pearson et al. 2003). Current interest into linkages between OSD and inflammation in the onset and development of the inflammatory response is growing; for example, inflammatory macrophages release glutathionylated peroxiredoxin-2, which then acts as a 'danger signal' to trigger the production of tumor necrosis factor-alpha (Salzano et al. 2014). The ratio of cysteine/glutathione, used as a redox imbalance marker, was significantly associated with a higher risk of mortality (adjusted HR = 1.92; 95% CI: 1.39–2.64), being independent of and additive to the inflammatory burden (monitored with high-sensitivity C-reactive protein measurements) in patients with coronary artery disease (Patel et al. 2016). Studies on the effectiveness of antioxidants in reversing disease risk have produced somewhat mixed results. For example, several double-blind interventional trials in humans showed that a treatment with free-radical-scavenging antioxidants presented with limited evidence for human health benefits (Lonn et al. 2005; Omenn et al. 1996; Williams and Fisher 2005).

Co-occurring redox imbalance and an inflammatory response have been also documented in human studies of environmental chemical health effects, such as polyaromatic hydrocarbons, metals or dioxins. These xenobiotics have been shown to induce immunotoxicity involving the chronic activation of xenobiotic receptors, such as the aryl hydrocarbon receptor (AHR) pollutant-sensor system, while the KEAP1-NRF2 system has been shown to promote protective effects against the development of pollutant – induced immunotoxic diseases (Suzuki et al. 2020). Acute or chronic exposures to xenobiotics may perturb immune response and resolution systems via cell death or aberrant signal transduction.

In the process of inflammatory activation of macrophages infected by biological or chemical agents, intermediate products of tricarboxylic acid (TCA) cycle, such as citrate and itaconate would continuously accumulate to promote anti-inflammatory processes by suppressing persistent inflammation during its resolution stage via inhibition of pro inflammatory genes. Itaconate is a key intermediate metabolite derived from *cis*-aconitate decarboxylation mediated by immune response gene 1 (IRG-1), or aconitate decarboxylase 1 (ACOD1) in mitochondrial matrix (Murphy and O'Neill 2018). Aconitate, is part of the Krebs citric acid energy production cycle and involved in energy metabolism and it cycles at the 8-h frequency, a third harmonic of circadian periodicity, based on mouse liver data (Krishnaiah et al. 2017). A time differentiating effect of dietary-induced pesticide toxicity on the levels of *cis*-

aconitate was observed by being higher in the evening period than in the morning (Ioannou et al. 2022).

Overall, redox imbalance as a result of χρόνος-modulating effects of external insults has not received much attention, albeit there is much literature on the immunomodulating effects of environmental chemicals, such as metals, including immunosuppression or stimulation of immune cell activity. Impaired immune activity has been associated with higher susceptibility to infections and lower immunoglobulin levels for those exposed to metals, such as, lead, when compared to the nonexposed group (Ewers et al. 1982). As such, chronic inflammatory response, hypersensitivity, allergies and autoimmunity have been reported as adverse biological effects of environmental chemical exposures. Detoxifying genes and antioxidant enzyme systems are activated upon environmental stressor-induced oxidative stress (ROS); such ROS and electrophiles are sensed by KEAP1, while NRF2 system activates the expression of phase 2 detoxifying enzymes like GSTs, UGTs, SULTs that aid in the activation of phase 3 transporters (ATP-binding cassette (ABC)). Many drugs or their reactive electrophilic metabolites, formed in phase I metabolism reactions by CYP enzymes, are detoxified by phase II conjugating enzymes. NRF2 impacts on the innate immune response by preventing the expression of IL6 and IL1b, and thereby suppressing inflammation by inducing the expression of antioxidant genes that quench ROS (Mittal et al. 2014; Suzuki et al. 2020). It is also known that oxidative stress may activate transcription factors such as NF-kB that induce the expression of proinflammatory genes (Suzuki et al. 2020).

5. The temporal dimensions of oxidative stress

In a naturally functioning core clock being in close connection with peripheral clocks, circadian rhythmicity harmonically dictates human physiology and the cycling of regular biological processes. But what happens when exogenous agents (chemical, physical, microbiological) are absorbed by the human body, impacting on the circadian clock system, or on specific biological processes or both? Chronotherapy and chronobiology are established research fields that attempt to provide answers to research questions developed around the above-mentioned scientific question. It is promising that certain drugs with narrow therapeutic index and unfavourable toxicity profile are currently used in chrono-modulated chemotherapy of cancer (Lévi et al. 1997). Better understanding the temporal dynamics of disease process may be of fundamental importance in a personalized medicine approach. Personalized medicine / personalized prevention schemes rely on the characterization of individuals' phenotypes (e.g., lifestyle data, metabolomic profiles, etc.) and genotypes (genetic markers) to determine their predisposition to diseases and to deliver disease prevention and prediction at the right time (Ruskovska et al. 2021).

Oxidative stress and/or damage, together with inflammation, are prime examples of reversible and proportional disease process models, as they chronologically appear or respond to an exposure or treatment in a relatively short time, allowing for the detailed temporal monitoring of stress/damage biological processes and their resolution (Fishbein et al. 2021; Serhan 2014) (Fig. 1). Such biological phenomena may be characterized by short(er) etiologic time intervals (ETI) required to comprehensively study the temporal disease dynamics spectrum than the longer ETI typically needed to study chronic disease outcomes. The ETI is an entity with units of time that defines the approximate time course of the biological effect(s), depending on the characteristics of the disease process model (e.g., reversible vs irreversible disease process). The ETI of an environmental/occupational exposure and effect association causing a reversible disease process, such as OSD, will be defined by the half time of repair, which represents the time required for the affected biological system to recover approximately 50% of the damage. It has been suggested that five half-times of repair would remove 97% of the damage present at the start of the time interval (Smith and Kriebel 2010). A dynamic behavior of disease process models is anticipated for all diseases in which resolution/recovery mechanisms may be

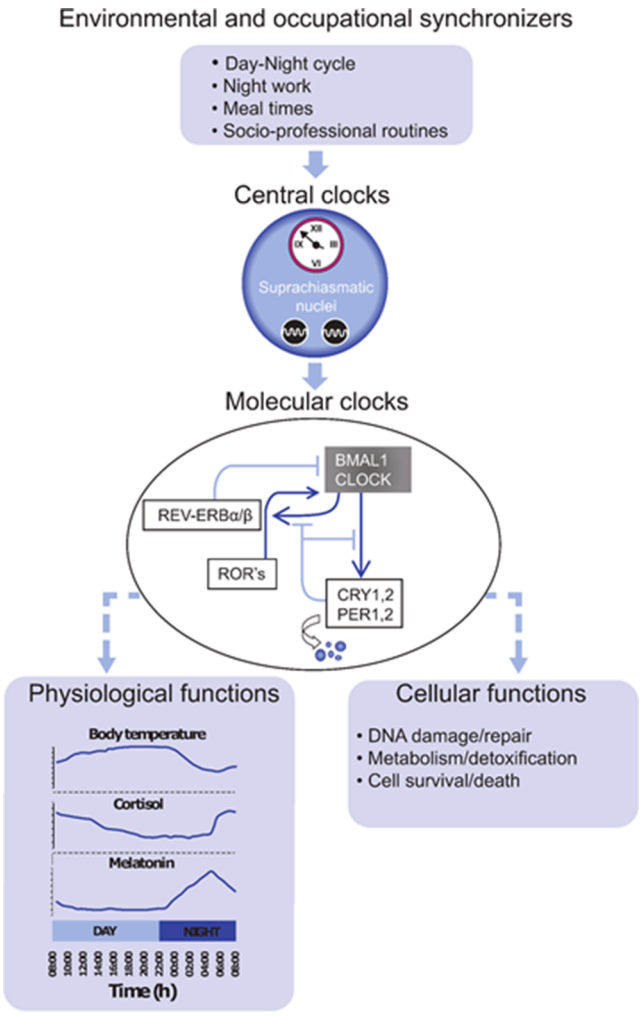

Fig. 5. Environmental and occupational stressors, such as dark-light cycle, occupation (i.e., night shift work), nutrition and socio-professional routines may influence central clock function located at the suprachiasmatic nucleus (SCN). The SCN then through regulation of the expression of the core molecular clock genes affects certain key physiological functions and cellular processes, including oxidative stress/damage, metabolism and inflammation, among others.

concurrently operating with the early-stage phases of the tissue damage process (e.g., inflammatory/oxidative damage), often leading to chronic disease outcomes, like, low back pain, cancer, or cardiovascular diseases, etc. Typical examples of such dynamically oscillating proportional and reversible disease models would be the proportional dosing effects of pesticides on the inhibition of cholinesterase enzyme, leading to the inhibition of cholinesterase and subsequent accumulation of acetylcholine, resulting in a cascade of symptomatic events in cases of organophosphate or carbamate poisoning (Smith and Kriebel 2010). Another example of reversible models would be the increasingly proportional use of cigarette packs per day that has been associated with the severity of respiratory outcomes. A two-stage mechanistic model of toxicity is typically composed of: stage I, where the absorption-distribution-metabolism patterns of external environmental cues results in the generation of highly reactive metabolites and free radicals attacking cellular macromolecules and inflicting tissue injury initiation, while stage II is composed of either tissue damage regression leading to repair or inhibition of tissue repair via progression of tissue damage (deBethizy and Hayes 2001; Mehendale 2005) (Fig. 5).

Damage reversibility or tissue repair is defined as the damage that comes to a steady-state for an average exposure, while the damage is

diminishing or disappearing when exposure diminishes or stops. Some environmental stressors (e.g., some chemicals) may instigate a reversible effect at low level exposures or short duration, but if these exposures increase in magnitude or in duration, then damage may be irreversible via cell death and other processes. For example, kidney effects of lead include both reversible renal tubular damage for short duration exposures, and when exposures become chronic, irreversible interstitial nephropathy develops (Smith and Kriebel 2010). High glucose in the body may adversely affect tissue repair capacity following exposure to environmental chemicals (Mehendale 2005). On the other hand, caloric restriction seems to facilitate and promote earlier onset and strong tissue repair response. The resolution of inflammatory processes is a recently coined process that could be used in analogy of the reversibility patterns observed in oxidative stress and damage processes (Serhan 2014). Moreover, dietary antioxidants may play role in reducing the oxidative ROS/RNS molecules. However, it is not clear how dietary factors may modulate the combinatory effects of circadian disruption and OSD.

Human defense to environmental stressors may utilize both non-enzymatic and enzymatic antioxidant systems to confront such resilience insults. The scientific substantiation of human health claims on the protection of body cells and molecules from oxidative damage, including photo-oxidative (UV-induced) damage, requires at least one appropriate marker of oxidative modification of the target molecule assessed *in vivo* in human studies. The protection of body cells and molecules, such as proteins, lipids and DNA from oxidative damage, including photo-oxidative damage is generally considered a beneficial physiological effect for humans, assuming that any significant oxidative modification of the target molecule is potentially harmful (Turck et al. 2018). A specific induction of antioxidant enzymes [e.g., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), haem oxygenase (HO)], or limiting the decrease in glutathione and glutathione/glutathione disulfide (GSH/GSSG) ratio, are considered a beneficial physiological effect, only if such changes provide (additional) cell/molecules protection o from oxidative damage; such protection from oxidative damage shall be demonstrated *in vivo* in humans (Turck et al. 2018). The same principle applies to non-specific changes observed in the overall antioxidant capacity of plasma assessed *in vivo* in humans using methods, such as TRAP, FRAP, TEAC, ORAC or FOX assays (Turck et al. 2018). It has been suggested that oxidative stress could participate in disease causation in three ways: i) as a sufficient cause (when oxidative stress alone can induce the disease); ii) as insufficient, but necessary component cause (oxidative stress will induce the disease only when combined with other component causes but, whatever the combination of causes is, oxidative stress has to be present); iii) as a non-necessary component cause, where oxidative stress contributes in the disease process for some patients, but for some others, disease process would develop this same condition with a different set of component causes, even in the absence of oxidative stress (Ghezzi 2020; Ghezzi et al. 2018; Rothman 1976). The inclusion of oxidative stress as a key characteristic of carcinogenicity is suggested to be used with caution, because non-carcinogens can also induce oxidative stress, unless it is found in combination with other key characteristics of carcinogenicity (Guyton et al. 2018).

What may be implied is that the interplay of antioxidants and prooxidants in the disease process may be complex enough, so that the ability to effectively monitor temporal patterns and trends associated with the evolution of biological events involved with disease onset, progression or severity may be severely hampered (Pandi-Perumal et al. 2013; Pérez et al. 2015; Rajendran et al. 2014). Unless selected biomarkers allow for the capturing of temporal dynamics, the observed outcomes may not capture well the etiologic end-products or effects lying in the exposure-effect-disease continuum.

6. Desynchronized circadian clock and oxidative stress phenomena

Human exposures to some environmental insults of physical, chemical, or biological origin would exhibit substantial within-subject variability as a result of recurrent lifestyle and behavioral patterns, and due to their relatively short half-lives of elimination. Such human exposures to a cocktail of environmental agents at unique windows of susceptibility would be implicated with perturbations in resilience and synchronization phenomena of endogenous health systems, and they would presumably impact downstream biological processes. It is often the case that the endogenous responses to such external stressors would operate within their own peripheral clock rhythm in synchronization with the central suprachiasmatic nucleus clock in the hypothalamus. These non-linear time-resolved exposures to environmental stressors would likely trigger a series of OSD stage phenomena that often go unnoticed, unless longitudinal data with repeated measures are collected and molecularly characterized. Recurring human exposures during critical life windows, and/or during circadian or diurnal (24-hour) varying rhythms would affect the magnitude and extent of the oxidative stress/damage process, i.e., specifically on the affected tissue response and its recovery rates and patterns. It would be prudent to clarify here that the 24-h diurnal rhythms may be either circadian or not, as in the case of stereotypic activities and behaviors (e.g., caffeine or lunch intake) that result in 24-h diurnal variation in xenobiotics exposures and effects (Dallmann et al. 2016a; Makris 2021; Arora et al., 2021); when the circadian clock is disrupted due to night time eating, insomnia, jet lag, night shift work and so on, some vital immune cells may be affected, leading to a decline in immunity and higher susceptibility to inflammation. Chemicals or xenobiotics, light (blue light or UV light) or noise and other environmental stressors would similarly adversely affect such internal biological processes (Fig. 2). External environmental exposures and their downstream internal biological effects may be linked by interfacial dynamic processes that operate their oscillating cycles in time (Makris 2021), and likely decomposed into two main networks of systems worth of studying collectively together; i) the exposure-dose continuum, and ii) the dose–effect continuum with emphasis on early or intermediate pathophysiological responses as a result of tissue damage.

Behaviorally-mediated patterns of abnormal time shifts in environmental exposures (e.g., diet, light at night, sleep loss, night shift work) would trigger the circadian system response of oxidative stress by influencing the suite of environmental stressor-metabolizing enzyme systems that govern absorption, distribution, metabolism and excretion processes. Such circadian activities of hepatic enzyme systems will be under the influence of the time of day exposures take place. It is worth mentioning here the importance of the chronotype status of individuals in the disease process (Semenova et al 2021; Strohmaier et al., 2018; Mondin et al., 2016). The human chronotype together with meal timing and circadian genes would interact with the effects of night shift work on cardiometabolic health (Strohmaier et al., 2018). Studies have also suggested that the chronotype may alter levels of oxidative stress in both bipolar and healthy subjects (Mondin et al., 2016). The perturbed state of biological damage is a dynamically complex state involving a myriad of damage-resolution steps as exposure continues or ceases, where such biomarkers of early-stage response are currently unknown and non-existent; crossing over to the disease state would represent a stable state where gold-standard markers of disease response are operational (Chen et al. 2012). The dynamical features of a system network approach in the disease etiology are imprinted onto two key characteristics of such temporal disease process models: i) the time course of the process (e.g., reversible, if recovery proceeds, after ceasing exposure), and ii) the response type (e.g., proportional, if response proportional to dose) (Smith and Kriebel 2010). The temporal dynamics of tissue concentration of environmental stressors (e.g., biomarkers of exposure to light) are the causal agents of the oxidative stress/damage and/or inflammatory response/effect, developing in time at the pace of

the slower rate limiting step(s), which are key step(s) in characterizing χρόνος-disease pathogenesis (Fig. 2).

It is important noting that both systemic and local proinflammatory cytokines show significant time of day variation (Hand et al. 2016). Key components of inflammatory response, such as macrophages (Early et al. 2018), natural killer cells (Labrecque and Cermakian 2015), T lymphocytes (Sutton et al. 2017), mast cells or eosinophils have autonomous peripheral clocks and characterized by a diurnal rhythmic activity. The diurnal patterns of salivary IL-6 and CRP in healthy young adults were distinct (Izawa et al. 2013). The majority of participants were asked to repeat the sampling procedure on two consecutive days to test the stability of the diurnal patterns. The salivary IL-6 levels peaked at awakening (~24 pg/mg), gradually declined from morning to noon, and peaked again at midnight (~20 pg/mg), before the participants went to sleep; the salivary CRP levels peaked at awakening, and they were lower during the daytime (Izawa et al. 2013). The χρόνος influence in the inflammatory process is important, where the magnitude and characteristics of the biological response to bacterial infections may vary, depending on the activity and functionality of the implicated peripheral circadian clock (Xie et al. 2020). It is well established that monitoring the timing/duration, number and magnitude of past environmental exposures could result in a differentiated susceptibility risk of cancer development, based on cancer's multi-stage activation theory (Vineis and Barouki 2022). Protective enzyme systems of antioxidant capacity seem to also operate under circadian rhythm (Wilking et al. 2013); prime examples are the type III peroxidases (PRXs) that remove peroxides from the cell or the Cu/Zn SOD enzyme systems, or the expression of GSH (Wilking et al. 2013). Literature suggests circadian oscillations for various biomarkers of oxidative damage; with the exception of urinary isoprostanes, a significant circadian rhythm was observed for uric acid, 8-OHdG and nitric oxide (NO) for healthy adults, peaking early in the evening (Kanabrocki et al. 2002; Manzella et al., 2015).

The expression of about 25 nuclear receptors including peroxisome proliferator-activated receptors (PPAR) family members and estrogen related receptors are rhythmic in nature, and they are well implicated with glucose and lipid metabolism (Sahar and Sassone-Corsi 2012b). Several enzyme systems are expressed in a daily rhythm, despite what was once believed that enzyme expression levels are constant, until induced (Baraldo 2008). Additionally, studies utilizing proteomics platforms demonstrated that some metabolic enzymes exhibit a cyclic in time behavior, despite constant transcript levels, indicating that post-transcriptional mechanisms are also involved in circadian regulation of enzyme activity (Robles et al. 2014). This was corroborated by metabolomics analyses in the liver (Adamovich et al. 2015; Eckel-Mahan et al. 2012). This peripheral clock functionality of liver enzymes may impact the metabolism and toxicity of absorbed environmental stressors, such as xenobiotics. Upon xenobiotic absorption, certain hepatic enzyme systems may be expressed and activated depending on the time of day, dosing, or class of absorbed xenobiotics. For example, the clearance mechanism for disinfectants/disinfection byproducts (e.g. trihalomethanes, THM) involves the CYP2E1-catalyzed biotransformation to carbon dioxide via phosgene hydrolysis and ROS production (Mathews et al. 1990). Pesticides are implicated with OSD phenomena, and they also undergo enzymatic cleavage catalyzed by a wide mixed system of P450 enzymes in intestinal tract and liver.

On the other hand, resolution and reversibility of such oxidative stress and/or inflammation processes may be governed by kinetically limited pro-resolving processes (Serhan 2014). As an example, acute inflammation may temporally and biologically proceed to chronic inflammation or not, depending on whether pro-resolving mechanisms are timely expressed. Anti-inflammatory processes are not the same as pro-resolving processes. Anti-inflammatory response deals with cessation of neutrophil infiltration, while resolution involves the active clearance of cellular debris including phagocytosis and macrophage recruitment. Much literature exists on *χρόνος*-based dietary interventions to reduce disease risk or to bring forward better cardiovascular health outcomes that are linked with the resolution process of oxidative stress/damage or inflammation phenomena (Dong et al. 2020). A series of theories have been developed to support this: i) The oxidative stress hypothesis supports decreased oxidative insult due to decreased energy intake causing mitochondria to produce fewer free radicals (Merry 2004). A second theory, the circadian rhythm hypothesis, is associated more with intermittent fasting than caloric restriction, indicating a mechanism unique to intermittent fasting, which focuses on the timing of when one can consume meals either within a day or a week. A third theory involves intermittent fasting with inducing a ketogenic state, where after 6–8 h of fasting, ketone levels (e.g., β-hydroxybutyrate) become detectable, signaling a switch from fat storage to fat utilization with decrease in low density lipoproteins (LDL) and increase in high-density lipoproteins (HDL) levels (Anton et al. 2018; Dashti et al. 2006; Dong et al. 2020).

7. Circadian disruption and oxidative stress/damage and inflammation: The case of night shift work

The public health consequences of circadian clock disruption are paramount, as about 20% of the European workforce is engaged in non-standard work schedules (Taiji and Mills 2019). According to the European Working Time Directive No. 2003/88/EC, "shift work means any method of organizing work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks" and "shift worker means any worker whose work schedule is part of shift work".

Systematic reviews and *meta*-analyses of epidemiological studies showed that night shift work is a risk factor for elevated blood pressure, hypertension, and cardiovascular disease, even after controlling for classical risk factors (Vyas et al. 2012). Energy intake of shift workers, compared to fixed day workers, did not statistically differ (standardized mean difference −0.04, 95%CI: −0.11, 0.03, p = 0.3) (Bonham et al. 2016). However, based on the dietary inflammatory index tool, the dietary quality of meals consumed by night shift workers was different from that of day shift workers, using U.S. NHANES data (Wirth et al. 2014). Shift work increased the risk of type II diabetes by 10%, based on a *meta*-analysis of 21 shift work studies that showed reduced insulin resistance and lower glucose tolerance during night shift work (Gao et al. 2020). Considering that oxidative stress/damage, along with inflammatory processes, may govern the early stages of a chronic disease process associated with night shift work, it is worth detailing these early-stage temporal dynamics of human biology (Fig. 2). The IARC recently declared night shift work as probably carcinogenic to humans (Group 2A) (IARC 2020), based mostly on experimental animal findings consistent with immunosuppression, chronic inflammation, and cell proliferation after alterations in light–dark schedule and also based on some evidence from human studies.

Alterations in light – dark schedule represent one of the most important types of circadian disruption. Circadian misalignment is a type of circadian disruption defined as the misalignment between the endogenous circadian system and the 24-h environmental/behavioral cycles. Under highly-controlled laboratory conditions of circadian misalignment, i.e., misalignment between the central circadian pacemaker and the 24-h environmental and behavioral cycles, a randomized cross-over trial suggested that short-term circadian misalignment increased 24-h blood pressure and inflammatory markers of CRP, TNF-α, resistin, and IL-6 in healthy adults (n = 14) (Morris et al. 2016). Hence, a scoping review was conducted to systematically map the research done in the area of night shift work effects on oxidative stress/damage and inflammation and to identify knowledge gaps in relation with the night shift work's temporal dimensions of redox imbalance pathogenesis.

Table 1
The characteristics of non-occupational studies on biomarkers of oxidative stress/damage and inflammation, including metabolic outcomes. The table also includes studies that focus on the diurnal variation in biomarkers of oxidative stress/damage and inflammation or metabolic in the presence of shift work patterns or not.

#	Authors	Matrix	Sampling times (night shift/day shift)	Outcomes	Main results	Study design	Sample size (n)	Population	Age	Sex
Oxidative stress/damage										
1	Aloui et al., 2017	Blood	Two times in day (07:00, 17:00), with recovery period of ≥ 36 h in-between. Blood taken before & 3 min after Time of day Yo-Yo Intermittent Recovery Test (YYIRT)	Malondialdehyde (MDA), creatine kinase, lactate dehydrogenase, high-density lipoprotein, total cholesterol, and triglycerides	Aerobic exercise (YYIRT) had diurnal variation with great result observed in evening improving hormonal, metabolic, and oxidative responses. Post-YYIRT MDA, glucose ($p < 0.01$), creatine kinase ($p < 0.01$), lactate dehydrogenase ($p < 0.05$), high-density lipoprotein ($p < 0.01$), total cholesterol ($p < 0.01$), and triglycerides ($p < 0.05$) were higher in the evening and increased after the YYIRT.	RCT	11	Students	21 ± 0.5	NA
2	Grew et al., 2014	Urine	24-h urine in four fractions covering 6 h each	8-oxo-7,8-dihydro-2′ deoxyguanosine (8-oxodG) and 8-oxo-7,8 dihydroguanosine (8-oxoGuo)	8-oxodG and 8-oxoGuo did not undergo diurnal variation. No significant difference in excretion of 8-oxodG & 8-oxoGuo between the 12-h diurnal and 12-h nocturnal state or between the four 6-h periods was found.	Repeated measures	23	Healthy adults	18–70	Both
3	Miyata et al., 2016	Urine	Four times a day (at 0:00, 06:00, 12:00, and 18:00)	8-hydroxydeoxyguanosine (8-OHdG), hexanoyl-lysine adduct (HEL), and total antioxidant power (TAO)	8-OHdG was lower in the younger age group in both controls and XPA patients. In the older age group, 8-OHdG increased in the XPA patients but not in controls, in which the robust peak was identified at 6:00. No significant difference in TAO between case and controls. Lacking the diurnal variation of TAO was observed in younger group.	Repeated measures	16	Xeroderma pigmentosum group A (XPA) patients	6–37	Both
4	Manzella et al. 2015*	Fasting blood	Samples collected every 4 h for a 24 h period (08:00 onwards). Fasting blood sampling performed at 07:00 beginning of morning shift after a day off	Comet assay, Base excision pair (BER) genes expression	A statistically significant circadian rhythm was validated only for BER's Ogg1 mRNA ($p < 0.05$) higher in morning, but not for Apex1 or XRCC1	Repeated measures	15	Healthy individuals	32 ± 4.3	Both
5	Koritala et al., 2021	Blood	Intravenous catheter at 3-hour intervals	Genomic DNA damage and comet assay-based DNA damage	Simulated night shift significantly altered circadian rhythmicity of genes involved in cancer hallmark pathways. Four genes, CRY1, CRY2, PER2, and NR1D2, lost their normal day shift rhythmicity after night shift schedule. Circadian expression DNA repair genes were dysregulated following night shift schedule	RCT (simulated day shift)	14	Healthy adults	22–34	NA
6	Nagata et al., 2017	Blood; Urine following night's sleep on day off.	Wake-up time on weekdays (n = 422) and during weekends (n = 120): (03:15–08:30), Bedtime weekdays (range:20:00–02:30).	8-isoprostane & 6-sulfatoxymelatonin, creatinine	Working night shift had 33.3% higher geometric mean 8-isoprostane levels than those who were not working night shift ($p = 0.03$) adjusted for confounders. Urinary 6-sulfatoxymelatonin levels were not associated with sleep habits or night shift work	Cohort	542	Women who attended a breast cancer mass screening at a general hospital	58.2 ± 9.4	Female

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Table 1 (*continued*)

#	Authors	Matrix	Sampling times (night shift/day shift)	Outcomes	Main results	Study design	Sample size (n)	Population	Age	Sex
Oxidative stress/damage and inflammation										
1	Mallard et al., 2020	Blood	Three fasting morning and three in the afternoon for type II diabetics (T2D) and a control group.	Inflammation markers (IL-6, 8, 10 and TNF-α), and oxidative stress markers of F2 isoprostanes, protein carbonyls (PC), total antioxidant capacity (TAC), glutathione peroxidase activity, IL-6, 8,10 and TNF-α	For all time-points combined, the coefficient of variation (CV) for inflammatory markers ranged from 64 to 92% and 7–31% for the oxidative stress/antioxidant markers. IL-6 was only marker showed differences in variability between groups with CV for control group 33% lower than for T2D ($p < 0.05$). Diurnal differences for PC in control group (23.7) were noted compared type 2 diabetic group (27.8), with the CV in the morning 11% less than the afternoon sessions ($p < 0.05$). There was not a significant difference on intra-individual biomarker CV between group when all timepoints were pooled together.	Nested (RCT) case control study with repeated measures	20	NR	52.8 ± 10.1 control group; 53.4 ± 8.1 T2D group	Both
2	Rangel-Zuñiga et al. 2017	Blood	Fasting morning	XBP1, IL6, MCP1, IL1B, TNF-a, UCP2, NFKB p65, NFKBIA, IKBKA, p91phox, p47phox, p40phox, SOD1, SOD2, GPX1, GPX4, GSR, PU.1, PPARG, MAPK8, MAPK14, RRM2, CDKN1A, MDM2, APEX1, DDB2, GADD45A, GADD45B, IL8, CXCL1, MMP9, MIF, CLOCK, BMAL1, CALR, BiP, IKBKB, p67phox, TXN, TXNRD1, NFE2L2, TP53, OGG1	Decrease in the expression of the oxidative stress-related gene GPX4 ($p < 0.001$) and an increase in the expression of CAT ($p < 0.001$) as a consequence of aging, independently of menopause. The expression of SOD1 gene was higher ($p = 0.041$) in post-menopausal women than in pre-menopausal group. GPX1 expression was lower ($p = 0.085$) in post-menopausal women than in pre-menopausal group.	Subgroup from control healthy group included in the CORDIOPREV study	76	Patients with coronary heart disease	46–55	Both
3	Ruskovska et al., 2021	Blood	6 times sampling at 4-hr intervals during a 24-hr, first sampling at 08:00, after overnight fasting.	Reactive Oxygen Metabolites (ROM), Biological Antioxidant Potency (BAP), Total thiols in proteins (TTP), high-sensitive C-Reactive Protein (CRP) and Uric Acid (UA).	A statistically significant effect between all six time points was observed for ROM (M: 0.002, F: 0.002), TTP (M: 0.003, F: 0.001) and UA (M: 0.002, F: 0.009); for BAP (F: 0.026) in females only. For CRP, no statistically significant difference was observed from time point 8 h to 12 h and 16 h, both sexes.	Repeated Measures	17	Healthy adults	24.9 ± 7.2 male; 21.7 ± 0.5 female	Both
Metabolic outcomes										
1	Skene et al., 2018	Blood	During 24-h constant routine following simulated night shift schedule	Plasma-circulating metabolites	24 metabolites (4 amino acids: ornithine,FDR = 0.023, arginine,FDR = 0.023, isoleucine,FDR = 0.018, and proline,FDR = $4.85x{\cdot}10^{-3}$, glycerophospholipids/ lysophosphatidylcholines & sphingolipids significantly shifted & most cases reversed (i.e., shifted by 12 h) rhythms under constant routine following simulated night-shift schedule. A group of 19 metabolites lost rhythmicity under constant routine following night-shift schedule.	RCT	14	Healthy adults	22–34	NA

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Table 1 (*continued*)

#	Authors	Matrix	Sampling times (night shift/day shift)	Outcomes	Main results	Study design	Sample size (n)	Population	Age	Sex
2	Joo et al., 2019	Blood	After 9–12 h of fasting	Dyslipidemia (based on total, high density lipoprotein, low-density lipoprotein, cholesterol, triglycerides), & shift work; Korean NHANES survey	Male: association of night shift work with dyslipidemia (OR = 1.53, 95% CI: 1.05–2.24). Female: No association of night work with dyslipidemia (OR: 1.12, 95%CI: 0.76 – 1.66).	Cross-sectional	5813	General population	30- ≥60	Both
3	Chalernvanichakorn et al., 2008	Blood	Fasting morning	Fasting blood glucose during the last six months, blood pressure during the last six months, and BMI (from the patient's records).	Good glycaemic control was significantly different between day workers (DSW) and night shift workers (NSW) (28.3% vs. 15.8%, p = 0.02) and a higher proportion of night shift workers had hypoglycemic symptoms compared to day workers (42.5% vs. 26.7%, p = 0.01).	Cross-sectional	240	Type II diabetics	46.6 + 8.5 (DSW); 45.6 + 8.5 (NSW)	NA
4	Manodpitipong et al., 2017	Blood	Fasting morning	Hemoglobin A1c (HbA1c) (from patient medical records)	Compared with day work, night-shift work was associated with poorer glycaemic control (p = 0.044). Night-shift workers had significantly higher Hb A1c levels compared with others, while there were no differences between day workers and unemployed participants (median 7.86% versus 7.24% versus 7.09%, respectively). Night shift work was statistically significant associated with HbA1c (b = 0.059, p = 0.044) vs. day shift workers	Cross sectional	249	Type II diabetics	56.4 ± 11	Both

* This Manzella et al 2015 sub study is independently mentioned within the Manzella et al 2015 study reported earlier in Table S1, hence, added also here in Table 2.

Table 2
The temporal profiling characteristics of shift work and markers of oxidative stress/damage and inflammation or metabolic outcomes among identified studies with longitudinal measurements from Tables 1, and Table S1 of this review.

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
Occupational studies											
Oxidative stress/damage											
1	Bhatti et al., 2016	217	223	Urine	For day shift workers, 1 day; Night shift workers, 2 consecutive shifts; Both followed by a day off.	After day shift for day shift workers; After one day off for night shift workers when at least two consecutive shifts were worked	Actigraph (Actiwatch-16, Mini Mitter, Bend, Oregon, USA) for sleep features	8-Oh-dG, 6-sulfatoxyme-latonin (aMT6s)	Nightshift workers during their day sleep periods excreted 83% ($p = 0.2$) and 77% ($p = 0.03$) of the 8-OH-dG that dayshift workers and themselves, respectively, excreted during their night sleep periods.	440	Health care workers (HCWs)
2	Ulas et al. 2013	70	70	Blood	8 h day shift; 16 h night shift	Before and after shift work	SenseWear Pro Armband™ Version 6.1 (BodyMedia, Inc., Pittsburgh, PA, USA)	Oxidative stress index (OSI), total antioxidant status (TAS) and total oxidant status (TOS)	TAS, TOS, and OSI levels either at baseline and the end of the shift ($p > 0.05$ for all) did not differ between night shift ordinary services (OS) and the night shift ICU group. Oxidative stress parameters (TAS, OSI, TOS) were significantly ($p < 0.05$ for all) increased at the end of the shifts in all OS and ICU nurses compared to the beginning of the shifts	140	Nurses
3	Buyukhatipoglu et al. 2010	30 (non-health care staff activities)	115 (16-h straight on call shift on site)	Blood	During shift work upon wake at 08:00 after an overnight fast; and then again near the end of shift, or after 16 h of consecutive work.	Before and after shift work at 8 AM and 12 PM.	-*	Total oxidant status (TOS), oxidative stress index (OSI), prolidase activity, and total antioxidant status (TAS)	Markers of oxidative stress, TOS, OSI were significantly increased in healthcare staff after prolonged work hours compared with non-health care hospital staff. Serum TAS levels decreased significantly in all at end of 16-h shift compared to pre-shift ($p < 0.0001$ for all healthcare staff). Serum prolidase activity significantly increased in all healthcare staff at end of shift compared to pre-shift ($p < 0.0001$ for all healthcare staff), but not in non-healthcare staff	145	HCWs
4	Ulas et al., 2012	60	60	Blood	8 h day shift; 16 h night shift	Before and at end of shifts	–	Total antioxidant status (TAS) and total oxidant status (TOS). Oxidative stress index (OSI)	Both in service and ICU nurses TAS, TOS, and OSI levels were not significantly different at the beginning or end of the shifts ($p > 0.05$).	120	Nurses

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Table 2 (*continued*)

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
5	Kazemi et al. 2018		30; shift-work 21-day cycle (7 nights, 7 day, & 7 off), every shift 12 h	Unstimulated saliva	Samples collected at the end of 7th night shift (6–7 a.m.) in all three cycles. Samples for melatonin collected at four times during night shift (19:00, 23:00, 03:00, and 07:00).	End of the 7th night shift in each cycle; Melatonin at 4 times	–	Catalase (CAT), total thiol molecules (TTG), and total antioxidant capacity (TAC), melatonin	No significant difference among various light conditions with regard to salivary biomarkers (catalase, total thiol molecules, and total antioxidant capacity) ($p > 0.5$).	30	Control room operators of Iran petrochemical complex
Oxidative stress/damage and inflammatory outcomes											
6	Reinhardt et al., 2019	21	17	Saliva	First sample collected in middle of shift cycle (Tue–Thur at 14:00 and 03:00 for day and night shift). Two other samples collected in same days, at bed and wake times (22:30 and 05:15 for day workers, 09:00 and 15:45 for night workers)	Middle of shift; At bed and wake up time	Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY).	Melatonin and cytokines (TNF and IL-1β)	Salivary TNF and IL-1β levels were similar for day and night workers, with higher daily production after awakening, in the morning hours for day workers and in the afternoon for night workers. Day and night workers produced similar amounts of salivary IL-6. Nevertheless, the daily variation pattern observed among day workers, with a peak after awakening, was absent among night workers.	38	Workers in sanitary metals industry
7	Morris et al., 2017	9 (circadian misalignment)	9 (circadian misalignment)	Blood	Every 4 h starting shortly after bedtime.	Two intravenous cannulae placed between 12:35PM and 4:35PM on wake period 1 in the circadian alignment protocol and between 12:35PM and 2:35PM on wake period 1 in the circadian misalignment protocol	Actiwatch Spectrum (Philips-Respironics, Murrysville PA)	C-reactive protein (hs-CRP), blood pressure and heart rate	Circadian misalignment increased 24-h hs-CRP by 11% ($p < 0.0001$). Circadian misalignment increased 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 1.4 mmHg and 0.8 mmHg, respectively (both $p \leq 0.038$). The misalignment-mediated increase in 24-h SBP was primarily explained by an increase in SBP during the wake period (+1.7 mmHg; $p = 0.017$), whereas misalignment-mediated increase in 24-h DBP was explained by an increase in DBP during the sleep opportunity (+1.8 mmHg; $p = 0.005$).	9	HCWs
8	Morris et al., 2016	14; Circadian misalignment (12-h inverted behavioral and	14; Circadian misalignment (12-h inverted behavioral and	Blood and Urine	Urine: shortly after scheduled wake time 24 h later in the circadian alignment	In a 24-hour period; Urine samples every 8 h;	Actiwatch Spectrum (Philips-Respironics)	Blood pressure, CRP, IL-6, TNF-α, resistin, 24-h urinary epinephrine/ norepinephrine,	Circadian misalignment increased blood pressure ($p < 0.0001$) and inflammatory markers	14	NR

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Table 2 (*continued*)

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
		environmental cycles for 3 days)	environmental cycles for 3 days)		protocol. Urine every 4 h: in wake episodes & once after 8-h sleep episodes. Blood every 4 h: in circa alignment protocol & in circa misalignment	Blood samples every 4 h		plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA) activity	CRP, TNF-α, resistin, and IL-6 ($p = 0.014$). Circadian misalignment increased urinary epinephrine by 82% during the sleep opportunities in which blood pressure and heart rate were measured ($p = 0.004$). Circadian misalignment decreased 24-h PAI-1 by 11% ($p = 0.014$). Circadian misalignment had no significant effect on 24-h tPA activity or its profile, regardless of exposure duration (all $p \geq 0.069$; $n = 6$).		
Metabolic and inflammatory outcomes											
9	Loef et al., 2019	93	503	Blood	Non fasting practices	Baseline and follow up after about 6 month period	–	BMI, waist circumference, cholesterol (total, HDL, LDL), triglycerides, hs-CRP	Shift workers had lower mean level of total cholesterol (5.54 mmol/L vs. 5.99 mmol/L, $p = 0.008$), LDL cholesterol (3.09 mmol/L vs. 3.49 mmol/L, $p = 0.002$). Compared to non-shift workers, shift workers' total cholesterol level was 0.38 mmol/L lower (95%-CI: −0.73 –-0.04) and LDL cholesterol was 0.34 mmol/L lower (95%-CI: −0.60 –-0.08). For all other metabolic risk factors, no differences were found (CRP was not affected by night shift work).	596	HCWs
10	Uetani et al., 2011	4079	2807	Blood	Between 09:00 and 15:00 throughout the study period	Over a 14-year period from 1991 to 2005-	–	Total cholesterol (TC) levels	Shift work was not associated with any of the six T-Cho endpoints in subjects who were overweight at entry ($p > 0.05$). In those who were not overweight at entry, alternating shift work was associated significantly with five serum T-Cho endpoints (>20%: OR = 1.15, 95% CI = 1.05, 1.26, $p = 0.002$; >25%: OR = 1.17, 95% CI = 1.05, 1.31, $p = 0.003$; >35%: OR =	6886	Steel company workers

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Table 2 (*continued*)

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
									1.24, 95% CI = 1.05, 1.46, p = 0.010; >40%: OR = 1.30, 95% CI = 1.06, 1.61, p = 0.014; >45%: OR = 1.31, 95% CI = 1.01, 1.71, p = 0.043.		
11	Karlsson et al., 2001	19,576	7909	Blood	Fasting morning	During the period 1992–1997	–	Total cholesterol and triglyceride, glucose concentrations and high-density lipoprotein (HDL), cholesterol	Age adjusted prevalence of metabolic risk factors (obesity, hypertension, and high triglycerides) were significantly higher among shift working compared with day workers ($p < 0.0001$).	27,485	General population
12	Lund et al., 2001	12	12	Blood and urine	Postprandial hormone and metabolic:(i) during daytime on a normal working day, (ii) during night-time at the beginning of a period of nightshift work, and (iii) during the daytime on return from night working to daytime working. Blood: Two baseline blood samples (at − 10 and 0 min) were taken and sampling continued for 9 h after consumption of meal; Urine: 4-hourly on two baseline days and the three test meal days	Before shift; Before and after meal	–	Postprandial hormone and metabolic responses to three standard mixed test meals, glucose, insulin, triacylglycerol (TAG) and non-esterified fatty acids, 6-alphatoxymelatonin (aMT6s) assay	Postprandial glucose tolerance deteriorated at commencement of night-shift work (day 1 vs day 9, $p < 0{\cdot}01$). Plasma insulin levels were significantly greater on the second night of night shifts ($p < 0.01$) compared with normal daytime working, but they had returned to normal daytime working patterns 2 days from the return from night-shift to daytime working (day 16). The postprandial TAG area under curve was significantly greater on the second day of night-shift work compared with normal daywork (day 1 vs day 9, $p < 0{\cdot}01$).	12	Workers on a British Antarctic Survey station at Halley Bay.
Non-occupational studies											
Oxidative stress/damage											
#	**Authors**			**Matrix**	**Duration of monitoring exposure/effect**	**Range of time points**	**Sensor**	**Outcome(s)**	**Main results**	**Sample size**	**Population**
13	Grew et al., 2014			Urine	1 day	4 times every 6 h	–	8-oxo-7,8-dihydro-2′ deoxyguanosine (8-oxodG) and 8-oxo-7,8 dihydroguanosine (8-oxoGuo)	8-oxodG and 8-oxoGuo did not undergo diurnal variation. No significant difference in excretion of 8-oxodG & 8-oxoGuo between the 12-h diurnal and 12-h nocturnal state or between the four 6-h periods was found.	23	Healthy adults
14	Miyata et al., 2016			Urine	18 h, at 0:00, 06:00, 12:00, and 18:00	4 times	–	8-hydroxydeoxyguanosine (8-OHdG), hexanoyl-	8-OHdG was lower in the younger age group in both controls and XPA patients.	16	Xeroderma pigmentosum

(*continued on next page*)

Table 2 (*continued*)

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
								lysine adduct (HEL), and total antioxidant power (TAO)	In the older age group, 8-OHdG increased in the XPA patients but not in controls, in which the robust peak was identified at 6:00. No significant difference in TAO between case and controls. Lacking the diurnal variation of TAO was observed in younger group.		group A (XPA) patients
15	Manzella et al. 2015			Fasting blood	1 day (08:00 onwards). Fasting blood sampling performed at 07:00 beginning of morning shift after a day off	6 times every 4 h	Minolta Chroma Meter CL-100 (Minolta Camera Company, Ltd. of Osaka, Japan)	Comet assay, Base excision pair (BER) genes expression	A statistically significant circadian rhythm was validated only for BER's Ogg1 mRNA ($p < 0.05$) higher in morning, but not for Apex1 or XRCC1	15	Healthy individuals
16	Aloui et al., 2017			Blood	Two times in day (07:00, 17:00), with recovery period of $\geq$ 36 h in-between. Blood taken before & 3 min after Yo-Yo Intermittent Recovery Test, YYIRT	2 times per 24-h before and after the YYIRT	–	MDA, creatine kinase, lactate dehydrogenase, high-density lipoprotein, total cholesterol, and triglycerides	Aerobic exercise (YYIRT) had diurnal variation with great result observed in evening improving hormonal, metabolic, and oxidative responses. Post-YYIRT MDA, glucose ($p < 0.01$), creatine kinase ($p < 0.01$), lactate dehydrogenase ($p < 0.05$), high-density lipoprotein ($p < 0.01$), total cholesterol ($p < 0.01$), and triglycerides ($p < 0.05$) were higher in the evening and increased after the YYIRT.	11	Students
17	Koritala et al., 2021			Blood	Intravenous catheter at 3-hour intervals	Following the 3 days on the simulated shift work schedule, subjects began a 24-hour constant routine protocol	–	Genomic DNA damage and comet assay-based DNA damage	Simulated night shift significantly altered circadian rhythmicity of genes involved in cancer hallmark pathways. Four genes, CRY1, CRY2, PER2, and NR1D2, lost their normal day shift rhythmicity after night shift schedule. Circadian expression DNA repair genes were dysregulated following night shift schedule	14	Healthy adults
18	Nagata et al., 2017			Blood; Urine following	Wake-up time on weekdays (n = 422) and during weekends	Following a night's	–	8-isoprostane & 6-sulfa-toxymelatonin, creatinine	Working night shift had 33.3% higher geometric mean 8-isoprostane levels	542	Women attended a breast cancer

(*continued on next page*)

Table 2 (*continued*)

#	Authors	#Day Shift subjects	#Night Shift subjects	Matrix	Duration of monitoring exposure/effect	Range of sampling points in time	Sensor	Outcome(s)	Significant effect sizes	Sample size	Profession
				night's sleep on day off.	(n = 120): (03:15–08:30), Bedtime weekdays (range:20:00–02:30).	sleep on a day off			than those who were not working night shift (p = 0.03) adjusted for confounders. Urinary 6-sulfatoxymelatonin levels were not associated with sleep habits or night shift work		mass screening at general hospital
Oxidative stress/damage and inflammation											
19	Ruskovska et al., 2021			Blood	1 day, first sampling at 08:00, after overnight fasting.	6 times every 4 h	–	Reactive Oxygen Metabolites (ROM), Biological Antioxidant Potency (BAP), Total thiols in proteins (TTP), high-sensitive C-Reactive Protein (CRP) and Uric Acid (UA).	A statistically significant effect between all six time points was observed for ROM (M: 0.002, F: 0.002), TTP (M: 0.003, F: 0.001) and UA (M: 0.002, F: 0.009); for BAP (F: 0.026) in females only. For CRP, no statistically significant difference was observed from time point 8 h to 12 h and 16 h, both sexes.	17	Healthy adults
Metabolic outcomes											
20	Skene et al., 2018			Blood	During 24-h constant routine following simulated night shift schedule	Every 1–3 h for metabolomics and cortisol and PER3 assays; For melatonin, hourly during the baseline day (18:30–21:30) and during the constant routine (18:30–01:30)	–	Plasma-circulating metabolites	24 metabolites (4 amino acids: ornithine, FDR = 0.023, arginine, FDR = 0.023, isoleucine, FDR = 0.018, and proline,FDR = $4.85x{\cdot}10^{-3}$, glycerophospholipids/ lysophosphatidylcholines & sphingolipids significantly shifted & most cases reversed (i.e., shifted by 12 h) rhythms under constant routine following simulated night-shift schedule. A group of 19 metabolites lost rhythmicity under constant routine following night-shift schedule.	14	Healthy adults

*No clear mentioning about the use of a sensor in this study.

7.1. Scoping review methodology

This scoping review protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols extension for scoping reviews (PRISMA-ScR) (Tricco et al. 2018), which was prepared by the research team and it is available upon request. The PICO (population, intervention, comparison, outcome) framework was used to conceptualize review questions. We performed a literature search of PubMed database from 2000 through March 2022, including hits retrieved on oxidative stress in human studies from the IARC (2020) monograph 124 on night shift work. The final search strategy for PubMed used the search string of "["oxidative damage"] AND ["chemical*"] OR ["shift work"] OR ["oxidative stress"] AND ["circadian*"]" (Fig. 3). We also used another search by adding "inflammation" in our search strategy ["oxidative damage"] AND ["chemical*"] OR ["shift work"] OR ["oxidative stress"] AND ["inflammation"] AND ["circadian*"]. The search strategy was prepared by the research team and further refined through team discussion. Review articles, commentaries/viewpoints, animal or *in vitro* studies or feasibility studies were excluded. Articles dealing with biomarkers other than those of both oxidative stress and inflammation in relation with night shift work, were excluded. Metabolic outcomes in relation with night shift work were also included in this work, as both oxidative stress and nitrosative stress have been implicated with cellular and extracellular metabolic events, or so called "metabolic stress" (Federico et al. 2007). The selected references were imported into Covidence, an electronic platform for systematic reviews and *meta*-analysis (Covidence 2019). To increase consistency, two reviewers screened the selected publications, discussed the results and amended the screening and data extraction procedure before beginning screening titles and abstracts and then full text. Two reviewers independently extracted data from each eligible article in Excel that was used to populate fields in Tables 1-2, and in Table S1. Any disagreements were resolved through discussion between the two reviewers.

7.2. Synthesis of results

We grouped the studies by setting (occupational or non-occupational), by types of outcomes (oxidative stress alone or coupled with inflammation, or coupled with metabolic outcomes), and summarized the type of settings, populations, study designs for each group, along with the measures used and broader findings for exposures (shift work types and patterns) and their outcomes (Tables 1-2, S1). Technical details of each publication that was retained for full text analysis can be found in Supplementary Information section (SI). After removal of duplicates and exclusion of ineligible hits, we considered 53 articles as eligible for this scoping review (Fig. 3).

7.2.1. Occupational studies

Out of these 53 articles, the majority (n = 41) took place in an occupational setting (Tables 1, S1). Most of the selected occupational health studies targeted on outcomes of oxidative stress/damage (n = 19), and their combination with inflammatory response (n = 10), or metabolic outcomes (n = 12) (Table S1).

Out of the 19 occupational studies that focused on biomarkers of oxidation stress / damage, about one fourth (n = 5) of them used repeated measures; the rest of studies were cross sectional, one intervention study and one case-control study. The vast majority of the shift work health studies (n = 15 studies) were conducted among health care workers (HCWs). The longitudinally repeated measures of the studies mostly focused on assessing the within worker variation in the beginning and end of shift periods, with mixed results of redox balance marker changes, such as, TAS, TOS, and OSI (Ulas et al. 2012; Ulas et al. 2013). Total antioxidant status (TAS) decreased, while serum prolidase activity increased towards the end of shift work compared with baseline levels (Buyukhatipoglu et al. 2010). In night shift work groups, antioxidant capacity as measured with TAC, TOS, OSI, SOD, or vitamin A/E was not significantly associated with night shift work ($p > 0.05$) (Gromadzińska et al. 2013; Khajehnasiri et al. 2014; Özdemir et al. 2013). In other studies, antioxidant capacity expressed by TAC, FRAP, or nitrite, or CAT, SOD was lower in night workers compared with day workers (Sharifian et al. 2005; Teixeiraet al. 2019). The biological antioxidant potential was significantly associated with the night shift working group and so was the glutathione peroxidase activity (Ebata et al. 2017; Gromadzińska et al. 2013). DNA damage has been extensively studied in shift work studies. By comparing levels of 8-OhdG, 8-oxoGua or other DNA adducts, increased DNA damage was observed in the night shift work group than those of the day shift work group (Ishihara et al. 2008; Kasai et al. 2001; Pavanello et al. 2019). Similar trends were observed with MDA or SOD (Casado et al. 2008; Casado et al. 2011). During their day sleep period, night shift workers excreted 83% ($p = 0.2$) and 77% ($p = 0.03$) of the DNA damage marker (8-OhdG) levels that day shift workers did, and compared to themselves during their night sleep periods, respectively (Bhatti et al. 2016; 2017); this was attributed to lower secretion of melatonin and lower DNA damage repair capacity during day sleep of night shift workers, hence, lower excretion of urinary DNA damage marker levels. More DNA breaks and less baseline DNA repair gene expression (e.g., for Ogg1) (Manzella et al. 2015) were observed in overnight on-site call workers, than those workers without overnight work patterns (Cheung et al. 2019).

The interplay between oxidation stress / damage and inflammation was also studied in relation with shift work patterns and types. There were 10 such occupational studies, but only three of them used repeated measures, with two of them being RCTs on circadian misalignment; the rest of studies were cross-sectional studies. The vast majority of these occupational health studies (n = 6 studies) on shift work were not conducted among health care workers, but in other professions, like police officers, airline personnel, metals industry. The two RCTs used as intervention a schedule of 12-h inverted behavioral and environmental cycles for 3 days; this circadian misalignment schedule increased 24-h blood pressure and hs-CRP, TNFa, IL6 and resistin (Morris et al. 2016; Morris et al. 2017). Both oxidative stress markers (SOD, oxidized LDL) together with markers of inflammatory response (TNFa, IFN-gamma, CRP) were found to be elevated in night shift workers (Demir et al. 2016). Lower antioxidant markers (e.g., TAC) and higher levels of markers of inflammatory response (TNFa, IFN-gamma, CRP) were similarly found in night shift workers, suggesting the interplay of oxidative stress and inflammatory response (El-Benhawy et al. 2021). However, there were several cross-sectional studies that did not show significant association between night shift work and inflammatory markers, such as CRP (Ramey et al. 2012; Viitasalo et al. 2015) or WBC (Nishitani and Sakakibara 2007; Viitasalo et al. 2015) or plasma pentraxin-3 (Demir et al. 2021) or salivary IL-6 and TNFa (Reinhardt et al. 2019). Immune tolerogenic functions and IL-10 expression were lower in night shift working groups, albeit night shift work did not alter the frequency of DEC205 + dendritic cells (Yang et al. 2019).

Similarly, the interplay of metabolic outcomes and inflammation was highlighted in 12 selected occupational studies. Only four of them used repeated measures; the rest were cross-sectional studies, while only four of them were conducted among health care workers. The longitudinal repeated measures-based studies included three cohorts and one panel study of postprandial hormone and metabolic outcomes. Surprisingly, shift workers' total and LDL cholesterol levels were lower than those of non-shift workers, especially for those working night shifts for more than 20 years, perhaps due to possible selection bias (Loef et al. 2019); no significant ($p > 0.05$) differences in metabolic risk factors, such as BMI and waist circumference, HDL cholesterol, triglycerides, and hs-CRP were observed between shift and non-shift workers (Loef et al. 2019). Other studies have shown an association between night shift work and total cholesterol levels, but only for those who were not overweight at entry (Uetani et al. 2011). In addition, night shift work was associated with age-adjusted prevalence of metabolic risk factors (e.

g., obesity, triglycerides, hypertension) (Karlsson et al. 2001) and hyperhomocysteinaemia (Zhang et al. 2020). Metabolic risk factors (e.g., blood pressure, obesity, total cholesterol) and flow-mediated dilation were elevated in night shift workers in cross-sectional studies (Qiao et al. 2020; Sookoian et al. 2007; Tarzia et al. 2012), while postprandial glucose tolerance deteriorated at beginning of night shift work schedule (Lund et al. 2001). Night shift work was associated with poorer glycaemic control and significantly higher HbA1c levels (Manodpitipong et al. 2017; Rizza et al. 2020). The 12-h rotating night shift group had significantly higher alkaline phosphatase enzyme levels (Khosravipour and Shah Mohammadi 2020). Shift work was also associated with WBC, CRP and monocyte, neutrophil counts (Lu et al. 2016; Rizza et al. 2020). Metabolomics revealed about 76 metabolites associated with shift work (Huang et al. 2021). Another metabolomics study showed the temporal shift of certain metabolites upon a simulated night shift schedule, such as for amino acids, sphingolipids or glycerophospholipids (Skene et al. 2018). However, the use of advanced -omics platforms to study the temporal evolution of shift work effects on oxidative damage or inflammation has not been widely used so far.

7.2.2. Non-occupational studies

While the majority of shift work-related studies was conducted in the workplace, a few studies (n = 13) were conducted in the general population or in controlled conditions (Table 1). The original publication (Bhatti et al., 2016) described both an occupational and a non-occupational study, thus, included twice in Tables 1, and Table S1, but counted once as an original publication. With the exception of three studies (Chalernvanichakorn et al., 2008; Joo et al., 2019; Nagata et al., 2017), the rest of studies monitored the diurnal variation of biomarkers of oxidative stress/damage (n = 6) with or without inflammatory markers (n = 2), or markers associated with metabolic outcomes (n = 2) with or without monitoring shift work patterns. In effect, an RCT simulating a night shift work schedule showed the dysregulation of DNA damage repair genes during night shift work schedule and the impaired circadian rhythmicity of genes involved in cancer hallmark pathways (Koritala et al. 2021). Another RCT followed the effect of administering an aerobic exercise program (yo-yo intermittent recovery test, YYIRT) in different times of the day on lipid peroxidation (MDA) (Aloui et al. 2017). Markers of DNA damage such as the 8-oxodG and 8-oxoGuo did not diurnally vary in healthy adults (Grew et al. 2014), while 8-OHdG showed a diurnally dictated peak at 18:00 in health adults (Miyata et al. 2016). Ogg1 mRNA base excision pair gene expression was characterized by a circadian rhythm, but this was not documented for other DNA damage repair genes (Manzella et al. 2015; Rangel-Zuñiga et al. 2017). Study results that combined makers of inflammation together with those of oxidative stress/damage using longitudinally repeated measures showed that some markers were characterized of a diurnal variation, such as, for uric acid, total thiols, but not for CRP (Ruskovska et al. 2021). For those studies focusing on metabolic outcomes, there was a study showing association between dyslipidemia and night shift work for males, but not for females (Joo et al. 2019). The scoping review had the limitation of considering only a single database for screening.

The temporal profiling characteristics of shift work and markers of oxidative stress/damage, inflammation, or metabolic outcomes among the identified studies with longitudinal measurements can be found in Table 2. It was estimated that the majority of selected studies in this review (~60%) did not use repeated measures in their study design (cross-sectional studies). It is possible that the average cross-sectional measurements of biomarkers of oxidative stress/damage or inflammation may or may not produce significant differences between night shift or day shift workers; nevertheless, in the presence of repeated measures, the daily variation patterns would facilitate the capturing of dampening or peak diurnal phenomena for circadian or oxidative stress and inflammatory markers. For example, the daily variation pattern in salivary IL-6 observed among day workers showing a peak after awakening was absent among night workers (Reinhardt et al. 2019), while similar effects on melatonin have been also observed. In the studies with longitudinal designs, about 30% of them used sensor(s) to monitor light exposure or sleep patterns (Table 2). The etiologic time interval used to profile the markers of oxidative stress, inflammation or metabolic outcomes was mostly in the order of a few hours to 24 h long; exception were the cohort studies that relied on a follow-up period of several months (Table 2).

8. Conclusions and prospects

This review critically examined the interplay of χρόνος and external stressors towards the delineation of oxidative stress and damage processes, including co-occurring inflammatory and metabolic processes. Although there is a tremendous progress in delineating the biological processes and mechanisms underlying the associations between environmental stressors and effects on redox balance using animal models and cell lines, an equally thorough investigation on the temporal dimensions of OSD in humans has yet to fully evolve. The black box of external determinants of the early-stage disease process, e.g., by focusing on redox imbalance phenomena remains poorly understood. It has been earlier shown that the study of temporally dynamic networks of biological systems would facilitate the detection/capture of critical transitions of early-warning signals of the pre-disease state. The temporal dynamics towards a perturbed state involves a myriad of steps, calling for a global search for 'network biomarkers' that are sensitive and responsive to changes in network's correlation matrix degree more than to actual values of single players (Chen et al. 2012). One may appreciate the importance of capturing and characterizing the etiologic time interval of the specific disease process in its entirety, including its possible resolution stage.

The early stages of reversible and proportional disease process models are invaluable, if one would be interested in shedding more light onto early-stage disease pathogenesis and its resolution processes. The case of night shift work in the OSD process was used as a prime example of a reversible and proportional disease process model, whose temporal profiling is much warranted for advancing the scientific fields of human toxicology, chronobiology, chrononutrition and environmental epidemiology. The circadian clock seems to modulate various redox imbalance processes and their biological pathways, but it is not always easy to predict the impact of the clock on the human toxicity patterns of external environmental stressors (e.g., shift work); this was particularly emphasized in this work using results from human studies. Further, this work is applicable to various groups of both occupational and environmental stressors that are characterized by a recurrent pattern in one's lifestyle/routine. As a case study, the scoping review on the circadian-disrupting effects of night shift work on the downstream oxidative stress and damage processes, including inflammation, revealed important methodological and study design considerations that would add much value, if accounted for in future human studies. It is noteworthy mentioning that only a minor fraction of all selected studies in this scoping review measured circadian rhythm markers, such as melatonin or its metabolite or cortisol. This reinforces the notion that circadian rhythm measurements are warranted, if we strive to improve our understanding of the chrono-modulated effects of environmental stressors on redox imbalance processes.

The implications of this work are of paramount importance for ongoing personalized medicine initiatives. In the USA (January 30, 2015), President Obama's Precision Medicine Initiative and the European Council's statement on personalized medicine (Fact Sheet 2015), both emphasized the need to better characterize individuals environment/occupation and gene profiles for the right person at the right time to deliver timely disease prevention or prediction. Towards these strategic initiatives, the human exposome concept and its exposomic tools (Haddad et al. 2022; Haddad et al. 2019; Wild 2012) provide us with the appropriate methodologies, tools, and technologies to accelerate the developments in the field of personalized medicine from the perspective

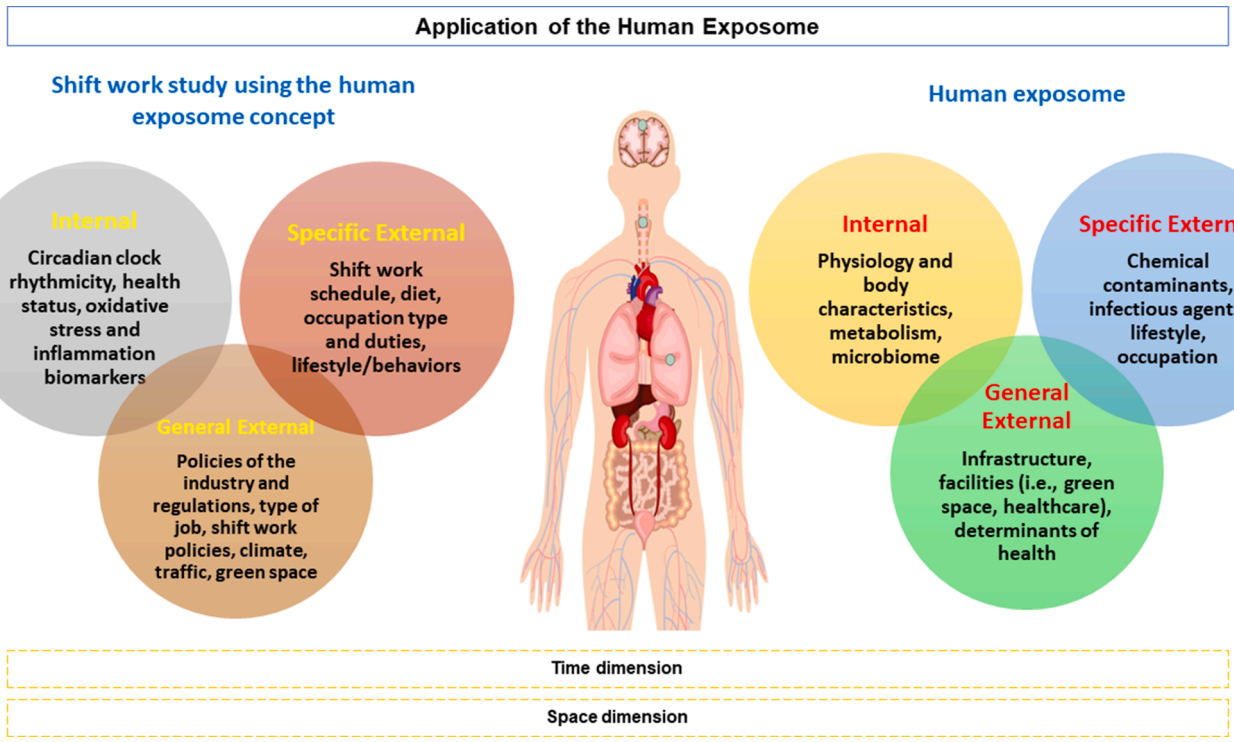

Fig. 6. The human exposome concept and its utility in the better understanding of the night shift work effects on early-stage process of disease pathogenesis, such as on oxidative stress/damage and inflammation. The main three exposome domains and the key components and groups of variables associated with each exposome domain in the application of the exposome concept in a night shift work human study are presented (left); the theoretical three exposome domains with indicative examples of their specific components and groups of variables are presented (right).

of personalized prevention. The human exposome concept presents a novel opportunity to comprehensively characterize all non-genetic environmental and occupational stressors throughout one's lifetime, including the endogenous response. Large population-based cohorts are an invaluable resource for investigating such causal links, but the temporal biodynamics and molecular resolution warranted to shed light on such reversible redox imbalance phenomena call for alternative study designs and tools. Such designs would consider nested within cohort studies or prospective panel studies where exposomic tools capable of monitoring shorter-term temporal profiles of exposure and effect are deployed (Haddad et al. 2019; Makris 2021; Vermeulen et al. 2020) (Fig. 6). As such, studying high-risk subpopulation groups, such as those with circadian misalignment or jet lag or excessive light exposure or irregular shift work represent tremendous opportunities to better understand the downstream redox imbalance processes. Animal models have been invaluable in offering new thinking and testing of hypotheses that delve into the association between environmental external stressors and the oxidative stress and tissue damage. Nevertheless, more attention could be drawn to the confirmatory role of animal studies, cell lines, and *in vitro* tests in scientific evidence from epidemiological studies. The resolution stage of the OSD process may be key in better understanding the redox imbalance process profiling over time of environmental insults on human health; these processes might be reversible if tackled early enough.

Overall, it appears that much progress has been made towards delineating the biological mechanisms and processes of OSD, as an early-stage disease process marker. However, an equally thorough investigation of the temporal dimensions of OSD, including inflammation, triggered by environmental and/or occupational insults, has yet to fully evolve in personalized medicine and in population studies utilizing state of the art exposomic tools. The same may also apply to delineating the effects of night shift work on OSD and other early-stage disease processes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

Heibati B. and K.C. Makris would like to acknowledge the partial funding support by the EXPOSOWORK project (OPPORTUNITY/0916/MSCA/0077), co-financed by the European Regional Development Fund and the Republic of Cyprus through the Research and Innovation Foundation. The proposal has also received the Seal of Excellence by the European Commission as submitted in the Marie Skłodowska-Curie action H2020-MSCA-IF-2018. The authors would like to thank Ms. Maria Spyrou (CUT) and Oda Astrid Foss (NIOH) for their technical support in designing the high-quality schematics of this critical review. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108048.

References

Adamovich, Y., Aviram, R., Asher, G., 2015. The emerging roles of lipids in circadian control. Biochim. Biophys. Acta. 1851 (8), 1017–1025.
Ali, S.S., Ahsan, H., Zia, M.K., Siddiqui, T., Khan, F.H., 2020. Understanding oxidants and antioxidants, Classical team with new players. J. Food. Biochem. 44, e13145.

Aloui, K., Abedelmalek, S., Chtourou, H., Wong, D.P., Boussetta, N., Souissi, N., 2017. Effects of time-of-day on oxidative stress, cardiovascular parameters, biochemical markers, and hormonal response following level-1 Yo-Yo intermittent recovery test. Physiol. Int. 104 (1), 77–90.

Anton, S.D., Moehl, K., Donahoo, W.T., Marosi, K., Lee, S.A., Mainous, A.G., Leeuwenburgh, C., Mattson, M.P., 2018. Flipping the Metabolic Switch, Understanding and Applying the Health Benefits of Fasting. Obesity (Silver Spring, Md). 26 (2), 254–268.

Arora, M., Curtin, P., Curtin, A., Austin, C., Giuliani, A., 2021. Environmental Biodynamics: A New Science of How the Environment Interacts with Human Health. Oxford University Press. https://doi.org/10.1016/j.envint.2021.106649.

Baraldo, M., 2008. The influence of circadian rhythms on the kinetics of drugs in humans. Expert Opin. Drug Metab. Toxicol. 4 (2), 175–192.

Baron, K.G., Reid, K.J., 2014. Circadian misalignment and health. Int. Rev. Psychiatry. 26 (2), 139–154.

Berger, E., Castagné, R., Chadeau-Hyam, M., Bochud, M., d'Errico, A., Gandini, M., Karimi, M., Kivimäki, M., Krogh, V., Marmot, M., Panico, S., Preisig, M., Ricceri, F., Sacerdote, C., Steptoe, A., Stringhini, S., Tumino, R., Vineis, P., Delpierre, C., Kelly-Irving, M., 2019. Multi-cohort study identifies social determinants of systemic inflammation over the life course. Nat. Commun. 10, 773.

Bhatti, P., Mirick, D.K., Randolph, T.W., Gong, J., Buchanan, D.T., Zhang, J., Davis, S., 2016. Oxidative DNA damage during sleep periods among nightshift workers. Occup. Environ. Med. 73 (8), 537–544.

Bhatti, P., Mirick, D.K., Randolph, T.W., Gong, J., Buchanan, D.T., Zhang, J., Davis, S., 2017. Oxidative DNA damage during night shift work. Occup. Environ. Med. 74 (9), 680–683.

Bonham, M.P., Bonnell, E.K., Huggins, C.E., 2016. Energy intake of shift workers compared to fixed day workers, A systematic review and meta-analysis. Chronobiol. Int. 33 (8), 1086–1100.

Buyukhatipoglu, H., Kirhan, I., Dag, O.F., Turan, M.N., Vural, M., Taskin, A., Aksoy, N., Sezen, Y., 2010. Oxidative stress increased in healthcare workers working 24-hour on-call shifts. Am. J. Med. Sci. 340 (6), 462–467.

Casado, Á., Castellanos, A., López-Fernández, M.E., Ruíz, R., García Aroca, C., Noriega, F., 2008. Relationship between oxidative and occupational stress and aging in nurses of an intensive care unit. Age (Dordr.) 30 (4), 229–236.

Casado, Á., Castellanos, A., López-Fernández, M.E., Ruiz, R., Imedio, E.L., Castillo, C., Fernández-Nieto, A.M., 2011. Determination of oxidative and occupational stress in palliative care workers. Clin. Chem. Lab. Med. 49 (3), 471–477.

Chalernvanichakorn, T., Sithisarankul, P., Hiransuthikul, N., 2008. Shift work and type 2 diabetic patients' health. J. Med. Assoc. Thailand 91, 1093.

Chen, L., Liu, R., Liu, Z.-P., Li, M., Aihara, K., 2012. Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers. Sci. Rep. 2, 342.

Cheung, V., Yuen, V.M., Wong, G.T.C., Choi, S.W., 2019. The effect of sleep deprivation and disruption on DNA damage and health of doctors. Anaesthesia 74 (4), 434–440.

Covidence. Covidence—Better Systematic Review Management, 2019. Available online, https://www.covidence.org/ (accessed on 14 March 2021).

Crouse, J.J., Carpenter, J.S., Song, Y.J.C., Hockey, S.J., Naismith, S.L., Grunstein, R.R., Scott, E.M., Merikangas, K.R., Scott, J., Hickie, I.B., 2021. Circadian rhythm sleep–wake disturbances and depression in young people, implications for prevention and early intervention. Lancet Psychiatry 8 (9), 813–823.

Dallmann, R., Okyar, A., Lévi, F., 2016. Dosing-Time Makes the Poison, Circadian Regulation and Pharmacotherapy. Trends Mol. Med. 22 (5), 430–445.

Dashti, H.M., Al-Zaid, N.S., Mathew, T.C., Al-Mousawi, M., Talib, H., Asfar, S.K., Behbahani, A.I., 2006. Long term effects of ketogenic diet in obese subjects with high cholesterol level. Mol. Cell. Biochem. 286 (1-2), 1–9.

deBethizy, J.D., Hayes, J.R., 2001. Metabolism, a determinant of toxicity. In: Hayes, A.W. (Ed.), Principles and Methods of Toxicology. Taylor and Francis, Philadelphia, pp. 77–136.

Demir, I., Toker, A., Zengin, S., Laloglu, E., Aksoy, H., 2016. Oxidative stress and insulin resistance in policemen working shifts. Int. Arch. Occup. Environ. Health 89 (3), 407–412.

Demir, I., Toker, A., Aksoy, H., Tasyurek, E., Zengin, S., 2021. The Impact of Shift Type on Oxidative Stress, Inflammation, and Platelet Activation. J. Occup. Environ. Med. 63, e127–e131.

Dong, T.A., Sandesara, P.B., Dhindsa, D.S., Mehta, A., Arneson, L.C., Dollar, A.L., Taub, P.R., Sperling, L.S., 2020. Intermittent Fasting, A Heart Healthy Dietary Pattern? Am. J. Med. 133 (8), 901–907.

Early, J.O., Menon, D., Wyse, C.A., Cervantes-Silva, M.P., Zaslona, Z., Carroll, R.G., Palsson-McDermott, E.M., Angiari, S., Ryan, D.G., Corcoran, S.E., Timmons, G., Geiger, S.S., Fitzpatrick, D.J., O'Connell, D., Xavier, R.J., Hokamp, K., O'Neill, L.A. J., Curtis, A.M., 2018. Circadian clock protein BMAL1 regulates IL-1β in macrophages via NRF2. Proc. Nat. Acad. Sci. USA 115, E8460–E8468.

Ebata, C., Tatsuta, H., Tatemichi, M., 2017. Potential objective biomarkers for fatigue among working women. J. Occup. Health. 59, 286–291.

Eckel-Mahan, K.L., Patel, V.R., Mohney, R.P., Vignola, K.S., Baldi, P., Sassone-Corsi, P., 2012. Coordination of the transcriptome and metabolome by the circadian clock. Proc. Nat. Acad. Sci. USA 109 (14), 5541–5546.

El-Benhawy, S.A., El-Tahan, R.A., Nakhla, S.F., 2021. Exposure to Radiation During Work Shifts and Working at Night Act as Occupational Stressors Alter Redox and Inflammatory Markers. Arch. Med. Res. 52 (1), 76–83.

El-Benna, J., Hurtado-Nedelec, M., Marzaioli, V., Marie, J.-C., Gougerot-Pocidalo, M.-A., Dang, P.-C., 2016. Priming of the neutrophil respiratory burst, role in host defense and inflammation. Immunol. Rev. 273 (1), 180–193.

EU Working Time Directive, Directive 2003/88/EC - working time. https://osha.europa.eu/en/legislation/directives/directive-2003-88-ec (accessed June 23, 2023).

Ewers, U., Stiller-Winkler, R., Idel, H., 1982. Serum immunoglobulin, complement C3, and salivary IgA levels in lead workers. Environ. Res. 29 (2), 351–357.

The White House Archives. FACT SHEET, President Obama's Precision Medicine Initiative. 30 January 2015. Available online, https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative (accessed on 1 May 2023).

Federico, A., Morgillo, F., Tuccillo, C., Ciardiello, F., Loguercio, C., 2007. Chronic inflammation and oxidative stress in human carcinogenesis. Int. J. Cancer. 121 (11), 2381–2386.

Fishbein, A., Hammock, B.D., Serhan, C.N., Panigrahy, D., 2021. Carcinogenesis, Failure of resolution of inflammation? Pharmacol. Ther. 218, 107670.

Franceschi, C., Zaikin, A., Gordleeva, S., Ivanchenko, M., Bonifazi, F., Storci, G., Bonafè, M., 2018. Inflammaging 2018, An update and a model. Semin. Immunol. 40, 1–5.

Frijhoff, J., Winyard, P.G., Zarkovic, N., Davies, S.S., Stocker, R., Cheng, D., Knight, A.R., Taylor, E.L., Oettrich, J., Ruskovska, T., Gasparovic, A.C., Cuadrado, A., Weber, D., Poulsen, H.E., Grune, T., Schmidt, H.H.H.W., Ghezzi, P., 2015. Clinical Relevance of Biomarkers of Oxidative Stress. Antioxid. Redox Signal. 23 (14), 1144–1170.

Gao, Y., Gan, T., Jiang, L., Yu, L.i., Tang, D., Wang, Y., Li, X., Ding, G., 2020. Association between shift work and risk of type 2 diabetes mellitus, a systematic review and dose-response meta-analysis of observational studies. Chronobiol. Int. 37 (1), 29–46.

Ghezzi, P., 2020. Environmental risk factors and their footprints in vivo – A proposal for the classification of oxidative stress biomarkers. Redox Biol. 34, 101442.

Ghezzi, P., Davies, K., Delaney, A., Floridi, L., 2018. Theory of signs and statistical approach to big data in assessing the relevance of clinical biomarkers of inflammation and oxidative stress. Proc. Natl. Acad. Sci. U.S.A. 115 (10), 2473–2477.

Gregor, M.F., Hotamisligil, G.S., 2011. Inflammatory Mechanisms in Obesity. Annu. Rev. Immunol. 29 (1), 415–445.

Grew, I.S., Cejvanovic, V., Broedbaek, K., Henriksen, T., Petersen, M., Andersen, J.T., Jimenez-Solem, E., Weimann, A., Poulsen, H.E., 2014. Diurnal variation of urinary markers of nucleic acid oxidation. Scand. J. Clin. Lab. Invest. 74 (4), 336–343.

Gromadzińska, J., Peplonska, B., Sobala, W., Reszka, E., Wasowicz, W., Bukowska, A., Lie, J.-A., 2013. Relationship between intensity of night shift work and antioxidant status in blood of nurses. Int. Arch. Occup. Environ. Health. 86 (8), 923–930.

Guyton, K.Z., Rieswijk, L., Wang, A., Chiu, W.A., Smith, M.T., 2018. Key Characteristics Approach to Carcinogenic Hazard Identification. Chem. Res. Toxicol. 31 (12), 1290–1292.

Haddad, N., Andrianou, X.D., Makris, K.C., 2019. A Scoping Review on the Characteristics of Human Exposome Studies. Curr. Pollut. Rep. 5 (4), 378–393.

Haddad, N., Andrianou, X., Parrish, C., Oikonomou, S., Makris, K.C., 2022. An exposome-wide association study on body mass index in adolescents using the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and 2013–2014 data. Sci. Rep. 12, 1–13.

Hand, L.E., Hopwood, T.W., Dickson, S.H., Walker, A.L., Loudon, A.S.I., Ray, D.W., Bechtold, D.A., Gibbs, J.E., 2016. The circadian clock regulates inflammatory arthritis. FASEB. J. 30 (11), 3759–3770.

Harrison, D., Griendling, K.K., Landmesser, U., Hornig, B., Drexler, H., 2003. Role of oxidative stress in atherosclerosis. Am. J. Cardiol. 91 (3), 7–11.

Huang, X., Chen, X., Zhao, S., Hou, J., Huang, L.i., Xu, J., Wang, W., He, M., Shen, O., Zhang, J., 2021. Metabolomic Profiles of Shift Workers and Day Workers, A Cross-Sectional Study. Obesity (Silver Spring, Md). 29 (6), 1074–1082.

Hussain, S.P., Hofseth, L.J., Harris, C.C., 2003. Radical causes of cancer. Nat. Rev. Cancer. 3 (4), 276–285.

International Agency for Research on Cancer. Night Shift Work. Lyon, France, © International Agency for Research on Cancer, 2020. For more information contact publications@iarc.fr.

Ioannou, E., Oikonomou, S., Efthymiou, N., Constantinou, A., Delplancke, T., Charisiadis, P., Makris, K.C., 2022. A time differentiated dietary intervention effect on the biomarkers of exposure to pyrethroids and neonicotinoids pesticides. iScience 26 (2), 105847.

Ishihara, I., Nakano, M., Ikushima, M., Hara, Y., Yoshimine, T., Haraga, M., Nakatani, J., Kawamoto, R., Kasai, H., 2008. Effect of work conditions and work environments on the formation of 8-OH-dG in nurses and non-nurse female workers. J. UOEH. 30 (3), 293–308.

Izawa, S., Miki, K., Liu, X., Ogawa, N., 2013. The diurnal patterns of salivary interleukin-6 and C-reactive protein in healthy young adults. Brain. Behav. Immun. 27, 38–41.

Jones, D., Sies, H., 2007. Oxidative stress. Encycl. Stress 3, 45–48.

Joo, J.H., Lee, D.W., Choi, D.W., Park, E.C., 2019. Association between night work and dyslipidemia in South Korean men and women, a cross-sectional study. Lipids. Health. Dis. 18, 75.

Kanabrocki, E.L., Murray, D., Hermida, R.C., Scott, G.S., Bremner, W.F., Ryan, M.D., Ayala, D.E., Third, J.L.H.C., Shirazi, P., Nemchausky, B.A., Hooper, D.C., 2002. Circadian variation in oxidative stress markers in healthy and type II diabetic men. Chronobiol. Int. 19 (2), 423–439.

Karlsson, B., Knutsson, A., Lindahl, B., 2001. Is there an association between shift work and having a metabolic syndrome? Results from a population-based study of 27,485 people. Occup. Environ. Med. 58, 747–752.

Kasai, H., Iwamoto-Tanaka, N., Miyamoto, T., Kawanami, K., Kawanami, S., Kido, R., Ikeda, M., 2001. Life style and urinary 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, effects of exercise, working conditions, meat intake, body mass index, and smoking. Jpn. J Cancer. Res. Gann. 92, 9–15.

Kazemi, R., Hemmatjo, R., Hamidreza, H., 2018. The effect of a blue enriched white light on salivary antioxidant capacity and melatonin among night shift workers: a field study. Ann. Occup. Environ. Med. 30, 61.

Khajehnasiri, F., Akhondzadeh, S., Mortazavi, S.B., Allameh, A., Khavanin, A., Zamanian, Z., 2014. Oxidative Stress and Depression among Male Shift Workers in Shahid Tondgouyan Refinery. Iran. J. Psychiatry. 9, 76–82.
Khan, A., 2012. Detection and quantitation of forty-eight cytokines, chemokines, growth factors, and nine acute phase proteins in healthy human plasma, saliva, and urine. J. Proteomics. 75 (15), 4802–4819.
Khosravipour, M., Shah Mohammadi, M., 2020. The effects of exposure to night shift work on liver function, a cross-sectional study with emphasis of alkaline phosphatase enzyme. Chronobiol. Int. 37 (1), 142–145.
Klaunig, J.E., Wang, Z., 2018. Oxidative stress in carcinogenesis. Curr. Opin. Toxicol. 7, 116–121.
Koritala, B.S.C., Porter, K.I., Arshad, O.A., Gajula, R.P., Mitchell, H.D., Arman, T., Manjanatha, M.G., Teeguarden, J., Van Dongen, H.P.A., McDermott, J.E., Gaddameedhi, S., 2021. Night shift schedule causes circadian dysregulation of DNA repair genes and elevated DNA damage in humans. J. Pineal. Res. 70, e12726.
Krishnaiah, S.Y., Wu, G., Altman, B.J., Growe, J., Rhoades, S.D., Coldren, F., Venkataraman, A., Olarerin-George, A.O., Francey, L.J., Mukherjee, S., Girish, S., Selby, C.P., Cal, S., Er, U., Sianati, B., Sengupta, A., Anafi, R.C., Kavakli, I.H., Sancar, A., Baur, J.A., Dang, C.V., Hogenesch, J.B., Weljie, A.M., 2017. Clock regulation of metabolites reveals coupling between transcription and metabolism. Cell. Metab. 25 (4), 961–974.
Kurutas, E.B., 2015. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress, current state. Nutr. J. 15, 1–22.
Labrecque, N., Cermakian, N., 2015. Circadian Clocks in the Immune System. J. Biol. Rhythms. 30 (4), 277–290.
Lévi, F., Zidani, R., Misset, J.-L., 1997. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. Int Org Cancer Chronother. Lancet (London, England). 350 (9079), 681–686.
Libby, P., 2006. Inflammation and cardiovascular disease mechanisms. Am. J. Clin. Nutr. 83 (2), 456S–460S.
Linet, M.S., Yin, Song-Nian, Gilbert, Ethel S., Dores, Graça M., Hayes, Richard B., Vermeulen, Roel, Tian, Hao-Yuan, Lan, Qing, Portengen, Lutzen, Ji, Bu-Tian, Li, Gui-Lan, Rothman, Nathaniel, 2015. A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers. Int. J. Cancer 137 (9), 2184–2197. https://doi.org/10.1002/ijc.29591.
Loef, B., Baarle, D.V., van der Beek, A.J., Beekhof, P.K., van Kerkhof, L.W., Proper, K.I., Gatfield, D., 2019. The association between exposure to different aspects of shift work and metabolic risk factors in health care workers, and the role of chronotype. PLoS One 14 (2), e0211557.
Lonn, E., Bosch, J., Yusuf, S., Sheridan, P., Pogue, J., Arnold, J.M., Ross, C., Arnold, A., Sleight, P., Probstfield, J., Dagenais, G.R., 2005. Effects of long-term vitamin E supplementation on cardiovascular events and cancer, a randomized controlled trial. JAMA 293, 1338–1347.
Lu, L.-F., Wang, C.-P., Tsai, I.-T., Hung, W.-C., Yu, T.-H., Wu, C.-C., Hsu, C.-C., Lu, Y.-C., Chung, F.-M., Jean, M.-C., 2016. Relationship between shift work and peripheral total and differential leukocyte counts in Chinese steel workers. J. Occup. Health. 58 (1), 81–88.
Lund, J., Arendt, J., Hampton, S.M., English, J., Morgan, L.M., 2001. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. J. Endocrinol. 171, 557–564.
Makris, K.C., 2021. Desynchronized circadian clock and exposures to xenobiotics are associated with differentiated disease phenotypes, The interface of desynchronized circadian clock and exposures to xenobiotics would lead to adverse response and recovery. Bioessays 43 (11), 2100159.
Mallard, A.R., Hollekim-Strand, Siri Marte, Björk Ingul, Charlotte, Coombes, Jeff S., 2020. High day-to-day and diurnal variability of oxidative stress and inflammation biomarkers in people with type 2 diabetes mellitus and healthy individuals. Redox Rep. 25 (1), 64–69.
Manodpitipong, A., Saetung, S., Nimitphong, H., Siwasaranond, N., Wongphan, T., Sornsiriwong, C., Luckanajantachote, P., Mangjit, P., Keesukphan, P., Crowley, S.J., Hood, M.M., Reutrakul, S., 2017. Night-shift work is associated with poorer glycaemic control in patients with type 2 diabetes. J. Sleep. Res. 26 (6), 764–772.
Manzella, N., Bracci, M., Strafella, E., Staffolani, S., Ciarapica, V., Copertaro, A., Rapisarda, V., Ledda, C., Amati, M., Valentino, M., Tomasetti, M., Stevens, R.G., Santarelli, L., 2015. Circadian modulation of 8-oxoguanine DNA damage repair. Sci. Rep. 5, 13752.
Mathews, J.M., Troxler, P.S., Jeffcoat, A.R., 1990. Metabolism and distribution of bromodichloromethane in rats after single and multiple oral doses. J. Toxicol. Environ. Health. 30 (1), 15–22.
McEwen, B.S., Stellar, E., 1993. Stress and the individual: mechanisms leading to disease. Arch Intern. Med. 153, 2093–2101.
Mehendale, H.M., 2005. Tissue repair, an important determinant of final outcome of toxicant-induced injury. Toxicol. Pathol. 33 (1), 41–51.
Merry, B.J., 2004. Oxidative stress and mitochondrial function with aging–the effects of calorie restriction. Aging Cell 3 (1), 7–12.
Mittal, M., Siddiqui, M.R., Tran, K., Reddy, S.P., Malik, A.B., 2014. Reactive oxygen species in inflammation and tissue injury. Antioxid. Redox. Signal. 20 (7), 1126–1167.
Miyata, R., Tanuma, N., Sakuma, H., Hayashi, M., 2016. Circadian rhythms of oxidative stress markers and melatonin metabolite in patients with xeroderma pigmentosum group A. Oxid. Med. Cell. Longev. 2016, 1–5.
Mondin, M., Carta, A.R., Facci, L., 2016. Kynurenine pathway, therapeutic interventions and neurodegenerative diseases. J. Neuroimmunol. 301, 23–29.
Morris, C.J., Purvis, T.E., Hu, K., Scheer, F.A., 2016. Circadian misalignment increases cardiovascular disease risk factors in humans. Proc. Natl. Acad. Sci. USA 113, E1402–E1411.
Morris, C.J., Purvis, T.E., Mistretta, J., Hu, K., Scheer, F.A.J.L., 2017. Circadian Misalignment Increases C-Reactive Protein and Blood Pressure in Chronic Shift Workers. J. Biol. Rhythms. 32 (2), 154–164.
Murphy, M.P., O'Neill, L.A.J., 2018. Krebs Cycle Reimagined, The Emerging Roles of Succinate and Itaconate as Signal Transducers. Cell 174 (4), 780–784.
Nagata, C., Tamura, T., Wada, K., Konishi, K., Goto, Y., Nagao, Y., Ishihara, K., Yamamoto, S., 2017. Sleep duration, nightshift work, and the timing of meals and urinary levels of 8-isoprostane and 6-sulfatoxymelatonin in Japanese women. Chronobiol. Int. 34 (9), 1187–1196.
Nishitani, N., Sakakibara, H., 2007. Subjective poor sleep and white blood cell count in male Japanese workers. Ind. Health. 45 (2), 296–300.
Omenn, G.S., Goodman, G.E., Thornquist, M.D., Balmes, J., Cullen, M.R., Glass, A., Keogh, J.P., Meyskens Jr., F.L., Valanis, B., Williams Jr., J.H., Barnhart, S., Cherniack, M.G., Brodkin, C.A., Hammar, S., 1996. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J. Natl. Cancer. Inst. 88, 1550–1559.
Özdemir, P.G., Selvi, Y., Özkol, H., Aydın, A., Tülüce, Y., Boysan, M., Beşiroğlu, L., 2013. The influence of shift work on cognitive functions and oxidative stress. Psychiatry. Res. 210 (3), 1219–1225.
Pandi-Perumal, S.R., BaHammam, A.S., Brown, G.M., Spence, D.W., Bharti, V.K., Kaur, C., Hardeland, R., Cardinali, D.P., 2013. Melatonin antioxidative defense, therapeutical implications for aging and neurodegenerative processes. Neurotox. Res. 23 (3), 267–300.
Patel, R.S., Ghasemzadeh, N., Eapen, D.J., Sher, S., Arshad, S., Ko, Y.-a., Veledar, E., Samady, H., Zafari, A.M., Sperling, L., Vaccarino, V., Jones, D.P., Quyyumi, A.A., 2016. Novel Biomarker of Oxidative Stress Is Associated With Risk of Death in Patients With Coronary Artery Disease. Circulation 133 (4), 361–369.
Pavanello, S., Stendardo, M., Mastrangelo, G., Casillo, V., Nardini, M., Mutti, A., Campisi, M., Andreoli, R., Boschetto, P., 2019. Higher Number of Night Shifts Associates with Good Perception of Work Capacity and Optimal Lung Function but Correlates with Increased Oxidative Damage and Telomere Attrition. BioMed Res. Int. 2019, 1–10.
Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., Rifai, N., Smith, S.C., Taubert, K., Tracy, R.P., Vinicor, F., 2003. Markers of inflammation and cardiovascular disease, application to clinical and public health practice, A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107 (3), 499–511.
Pérez, S., Pereda, J., Sabater, L., Sastre, J., 2015. Redox signaling in acute pancreatitis. Redox. Biol. 5, 1–14.
Phillips, M.L., 2009. Circadian rhythms, Of owls, larks and alarm clocks. Nature 458 (7235), 142–144.
Prescott, S.L., 2013. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J. Allergy. Clin. Immunol. 131 (1), 23–30.
Qiao, H., Beibei, Z., Chong, T., Tieying, Z., Yuzhi, G., Jing, M., Davidson, P.M., 2020. Both frequency and duration of rotating night shifts are associated with metabolic parameters, a cross-sectional study. Sleep. Med. 71, 89–96.
Rajendran, P., Nandakumar, N., Rengarajan, T., Palaniswami, R., Gnanadhas, E.N., Lakshminarasaiah, U., Gopas, J., Nishigaki, I., 2014. Antioxidants and human diseases. Clin. Chim. Acta. 436, 332–347.
Ramey, S.L., Perkhounkova, Y., Moon, M., Budde, L., Tseng, H.-C., Clark, M.K., 2012. The effect of work shift and sleep duration on various aspects of police officers' health. Workplace Health. Saf. 60 (5), 215–222.
Rangel-Zuñiga, O.A., Cruz-Teno, C., Haro, C., Quintana-Navarro, G.M., Camara-Martos, F., Perez-Martinez, P., Garcia-Rios, A., Garaulet, M., Tena-Sempere, M., Lopez-Miranda, J., Perez-Jimenez, F., Camargo, A., 2017. Differential menopause-versus aging-induced changes in oxidative stress and circadian rhythm gene markers. Mech. Ageing. Dev. 164, 41–48.
Reinhardt, É.L., Fernandes, P.A.C.M., Markus, R.P., Fischer, F.M., 2019. Night work effects on salivary cytokines TNF, IL-1β and IL-6. Chronobiol. Int. 36 (1), 11–26.
Rizza, S., Longo, S., Piciucchi, G., Romanello, D., Mavilio, M., Montagna, M., Coppeta, L., Martelli, E., Magrini, A., Federici, M., 2020. Carotid intimal medial thickness in rotating night shift is related to IL1β/IL6 axis. Nutr. Metab. Cardiovasc. Dis. 30 (10), 1826–1832.
Robles, M.S., Cox, J., Mann, M., Kramer, A., 2014. In-vivo quantitative proteomics reveals a key contribution of post-transcriptional mechanisms to the circadian regulation of liver metabolism. PLoS. Genet. 10 (1), e1004047.
Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., Merrow, M., 2007. Epidemiology of the human circadian clock. Sleep Med. Rev. 11 (6), 429–438.
Rothman, K.J., 1976. Causes. Am. J. Epidemiol. 104, 587–592.
Ruskovska, T., Beekhof, P., Velickova, N., Kamcev, N., Jansen, E., 2021. Circadian rhythm and time-of-day-effects of (anti)oxidant biomarkers for epidemiological studies. Free Radic. Res. 55 (7), 693–699.
Sahar, S., Sassone-Corsi, P., 2012. Regulation of metabolism, the circadian clock dictates the time. Trends Endocrinol. Metab. 23 (1), 1–8.
Salzano, S., Checconi, P., Hanschmann, E.-M., Lillig, C.H., Bowler, L.D., Chan, P., Vaudry, D., Mengozzi, M., Coppo, L., Sacre, S., Atkuri, K.R., Sahaf, B., Herzenberg, L. A., Herzenberg, L.A., Mullen, L., Ghezzi, P., 2014. Linkage of inflammation and oxidative stress via release of glutathionylated peroxiredoxin-2, which acts as a danger signal. Proc. Natl. Acad. Sci. USA 111 (33), 12157–12162.
Semenova, Y.A., Zakharenko, A.M., Solov'eva, T.I., Malyshkina, A.I., Kolesnikov, S.I., 2021. Protective properties of kynurenic acid in the experimental model of toxic hepatitis. Environ. Int. 171, 384–387.

Serhan, C.N., 2014. Pro-resolving lipid mediators are leads for resolution physiology. Nature 510 (7503), 92–101.
Sharifian, A., Farahani, S., Pasalar, P., Gharavi, M., Aminian, O., 2005. Shift work as an oxidative stressor. J. Circadian Rhythms 3, 15.
Sies, H., 1986. Biochemistry of oxidative stress. Angew. Chem. Int. Ed. Engl. 25 (12), 1058–1071.
Sies, H., 2017. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress, Oxidative eustress. Redox. Biol. 11, 613–619.
Sies, H., 2020. Oxidative stress, Concept and some practical aspects. Antioxidants 9, 852.
Skene, D.J., Skornyakov, E., Chowdhury, N.R., Gajula, R.P., Middleton, B., Satterfield, B. C., Porter, K.I., Van Dongen, H.P.A., Gaddameedhi, S., 2018. Separation of circadian- and behavior-driven metabolite rhythms in humans provides a window on peripheral oscillators and metabolism. Proc. Natl. Acad. Sci. USA 115 (30), 7825–7830.
Smith, T.J., Kriebel, D., 2010. A biological approach to environmental assessment and epidemiology. Oxford Univ. Press.
Sookoian, S., Gemma, C., Fernández Gianotti, T., Burgueño, A., Alvarez, A., González, C. D., Pirola, C.J., 2007. Effects of rotating shift work on biomarkers of metabolic syndrome and inflammation. J. Intern. Med. 261 (3), 285–292.
Strohmaier, J., Ramos-Rivera, A., Gilbert, J.S., Scholz, T.D., 2018. The role of the placenta in gestational diabetes mellitus, A review of the literature. Curr. Diabetes. Rep. 18, 132.
Sutton, C.E., Finlay, C.M., Raverdeau, M., Early, J.O., DeCourcey, J., Zaslona, Z., O'Neill, L.A.J., Mills, K.H.G., Curtis, A.M., 2017. Loss of the molecular clock in myeloid cells exacerbates T cell-mediated CNS autoimmune disease. Nat. Commun. 8, 1923.
Suzuki, T., Hidaka, T., Kumagai, Y., Yamamoto, M., 2020. Environmental pollutants and the immune response. Nat. Immunol 21 (12), 1486–1495.
Taiji, R., Mills, M.C., 2019. Non-standard Schedules, Work-Family Conflict, and the Moderating Role of National Labour Context, Evidence from 32 European Countries. Eur. Sociol. Rev. 36, 179–197.
Tarzia, P., Milo, M., Di Franco, A., Di Monaco, A., Cosenza, A., Laurito, M., Lanza, G.A., Crea, F., 2012. Effect of shift work on endothelial function in young cardiology trainees. Eur J Prev Cardiol. 19 (5), 908–913.
Teixeira, K.R.C., Dos Santos, C.P., de Medeiros, L.A., Mendes, J.A., Cunha, T.M., De Angelis, K., Penha-Silva, N., de Oliveira, E.P., Crispim, C.A., 2019. Night workers have lower levels of antioxidant defenses and higher levels of oxidative stress damage when compared to day workers. Sci. Rep. 9, 4455.
Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D.J., Horsley, T., Weeks, L., Hempel, S., Akl, E.A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M.G., Garritty, C., Lewin, S., Godfrey, C.M., Macdonald, M.T., Langlois, E.V., Soares-Weiser, K., Moriarty, J.o., Clifford, T., Tunçalp, Ö., Straus, S.E., 2018. PRISMA Extension for Scoping Reviews (PRISMA-ScR), Checklist and Explanation. Ann. Intern. Med. 169 (7), 467–473.
Turck, D., Bresson, J.-L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K.I., Mangelsdorf, I., McArdle, H.J., Naska, A., Neuhäuser-Berthold, M., Nowicka, G., Pentieva, K., Sanz, Y., Sjödin, A., Stern, M., Tomé, D., Van Loveren, H., Vinceti, M., Willatts, P., Martin, A., Strain, J.J., Heng, L., Valtueña Martínez, S., Siani, A., 2018. Guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health, (Revision 1). EFSA J. Eur. Food. Saf. Auth. 16 (1), e05136.
Uetani, M., Sakata, K., Oishi, M., Tanaka, K., Nakada, S., Nogawa, K., Suwazono, Y., 2011. The influence of being overweight on the relationship between shift work and increased total cholesterol level. Ann. Epidemiol. 21 (5), 327–335.
Ulas, T., Buyukhatipoglu, H., Kirhan, I., Dal, M.S., Eren, M.A., Hazar, A., Demir, M.E., Aydogan, T., Karababa, F., Uyanikoglu, A., Kurkcuoglu, I.C., 2012. The effect of day and night shifts on oxidative stress and anxiety symptoms of the nurses. Eur. Rev. Med. Pharmacol. Sci. 16, 594–599.
Ulas, T., Buyukhatipoglu, H., Kirhan, I., Dal, M.S., Ulas, S., Demir, M.E., Eren, M.A., Ucar, M., Hazar, A., Kurkcuoglu, İ.C., Aksoy, N., 2013. Evaluation of oxidative stress parameters and metabolic activities of nurses working day and night shifts. Rev. Esc. Enferm. USP. 47 (2), 471–476.
van 't Erve, T.J., Kadiiska, M.B., London, S.J., Mason, R.P., 2017. Classifying oxidative stress by F2-isoprostane levels across human diseases: A meta-analysis. Redox Biol. 12, 582–599. https://doi.org/10.1016/j.redox.2017.03.024 [Epub 2017 Mar 28].
Vermeulen, R., Schymanski, E.L., Barabási, A.-L., Miller, G.W., 2020. The exposome and health: Where chemistry meets biology. Science 367 (6476), 392–396.
Viitasalo, K., Puttonen, S., Kuosma, E., Lindström, J., Härmä, M., 2015. Shift rotation and age - interactions with sleep-wakefulness and inflammation. Ergonomics 58 (1), 65–74.
Vineis, P., Barouki, R., 2022. The exposome as the science of social-to-biological transitions. Environ. Int. 165, 107312.
Vyas, M.V., Garg, A.X., Iansavichus, A.V., Costella, J., Donner, A., Laugsand, L.E., Janszky, I., Mrkobrada, M., Parraga, G., Hackam, D.G., 2012. Shift work and vascular events, systematic review and meta-analysis. BMJ 345 (jul26 1), e4800.
Wang, C., Lutes, L.K., Barnoud, C., Scheiermann, C., 2022. The circadian immune system. Sci Immunol 7, eabm2465.
Wild, C.P., 2012. The exposome, from concept to utility. Int. J. Epidemiol. 41 (1), 24–32.
Wilking, M., Ndiaye, M., Mukhtar, H., Ahmad, N., 2013. Circadian rhythm connections to oxidative stress, implications for human health. Antioxid Redox Signal. 19 (2), 192–208.
Williams, K.J., Fisher, E.A., 2005. Oxidation, lipoproteins, and atherosclerosis, which is wrong, the antioxidants or the theory? Curr. Opin. Clin Nutr. Metab. Care. 8 (2), 139–146.
Wirth, M.D., Burch, J., Shivappa, N., Steck, S.E., Hurley, T.G., Vena, J.E., Hébert, J.R., 2014. Dietary inflammatory index scores differ by shift work status, NHANES 2005 to 2010. J. Occup. Environ. Med. 56, 145–148.
Xie, M., Tang, Q., Nie, J., Zhang, C., Zhou, X., Yu, S., Sun, J., Cheng, X., Dong, N., Hu, Y., Chen, L., 2020. BMAL1-Downregulation Aggravates Porphyromonas Gingivalis-Induced Atherosclerosis by Encouraging Oxidative Stress. Circ. Res. 126, e15–e29.
Yang, H., Yang, J., Cheng, H., Cao, H., Tang, S., Wang, Q., Zhao, J., Li, B., Ding, Y., Ma, C., 2019. Probiotics ingestion prevents HDAC11-induced DEC205+ dendritic cell dysfunction in night shift nurses. Sci. Rep. 9, 18002.
Zhang, S., Wang, Y., Li, Q., Wang, Z., Wang, H., Xue, C., Zhu, Y., Guan, W., Yuan, J., 2020. Different exposure metrics of rotating night shift work and hyperhomocysteinaemia among Chinese steelworkers, a cross-sectional study. BMJ Open 10 (12), e041576.