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Working Conditions and Technostress in the Workplace: Physiological and Psychological Correlates

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Helena Christina Kaltenegger

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Erstes Gutachten:	*Prof. Dr. Matthias Weigl*
Zweites Gutachten:	*Prof. Dr. Nicolas Rohleder*
Drittes Gutachten:	*Prof. Dr. Karl-Heinz Herbinger*
weiteres Gutachten:	*Prof. Dr. Stefanie Heinze*

Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung:	21.10.2024

Affidavit

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List of Abbreviations

CRP	C-reactive protein
ICTs	Information and communication technologies
HPA axis	Hypothalamic-pituitary-adrenocortical axis
Hs-CRP	High-sensitivity C-reactive protein

Abstract (English)

Working conditions in the digital era bear risks for stress experience and adverse health outcomes. Despite growing scientific interest in *technostress*, that is stress due to the use of digital technologies, the current evidence base is limited by a lack of studies on physiological effects and prospective designs. Low-grade inflammation and the hypothalamic-pituitary-adrenocortical axis are two biological mechanisms through which chronic stress, such as work stress, "gets under the skin" and can lead to disease. This cumulative dissertation comprising five publications investigated associations of working conditions including technostress with physiological and psychological outcomes in employees, particularly healthcare professionals. A systematic review with meta-analysis and two original studies in real-world occupational settings were conducted. As predictors, self-reported general work stressors (e.g., job demands, control) as well as technostressors (e.g., interruptions, multitasking, information overload) and as outcomes, biomarkers (i.e., inflammatory markers, hair cortisol) as well as psychological sequelae (i.e., burnout symptoms) were assessed. Results were mixed for associations between general working conditions and low-grade inflammation and statistically non-significant for associations between technostressors and low-grade inflammation (Papers II–V). However, technostress was prospectively negatively associated with hair cortisol concentration (Paper V). Furthermore, technostress was significantly associated with burnout symptoms in cross-sectional (Paper IV) but not in prospective analyses (Paper V). Overall, the findings provide novel insights into the physiological and psychological correlates of work stress and first evidence for differential effects of technostress. More prospective studies are needed to validate the results, further elucidate how digitalized working conditions affect employees' health, and develop targeted measures for occupational health and safety.

Zusammenfassung (Deutsch)

Arbeitsbedingungen im digitalen Zeitalter bergen Risiken für Stresserleben und gesundheitliche Beeinträchtigungen. Trotz des zunehmenden wissenschaftlichen Interesses an *Technostress*, d.h. Stress aufgrund der Nutzung digitaler Technologien, ist die aktuelle Evidenzbasis durch einen Mangel an Studien zu physiologischen Effekten und prospektiven Designs begrenzt. Unterschwellige Entzündung und die Hypothalamus-Hypophysen-Nebennierenrinden-Achse sind zwei biologische Mechanismen, durch die chronischer Stress, wie Arbeitsstress, „unter die Haut geht" und zu Krankheiten führen kann. Diese kumulative Dissertation bestehend aus fünf Publikationen untersuchte Zusammenhänge von Arbeitsbedingungen, einschließlich Technostress, mit physiologischen und psychologischen Folgen bei Arbeitenden, insbesondere Gesundheitspersonal. Eine systematische Übersichtsarbeit mit Meta-Analyse und zwei Originalstudien in realen Arbeitskontexten wurden durchgeführt. Als Prädiktoren wurden selbst-berichtete allgemeine Arbeitsstressoren (z.B. Arbeitsanforderungen, Kontrolle) sowie Technostressoren (z.B. Unterbrechungen, Multitasking, Informationsüberflutung) und als abhängige Variablen Biomarker (d.h. Entzündungsmarker, Haar-Cortisol) sowie psychologische Folgen (d.h. Burnout-Symptome) erfasst. Die Ergebnisse waren uneinheitlich für Zusammenhänge zwischen allgemeinen Arbeitsbedingungen und unterschwelliger Entzündung und statistisch nicht signifikant für Zusammenhänge zwischen Technostressoren und unterschwelliger Entzündung (Artikel II–V). Technostress war jedoch längsschnittlich negativ mit Haar-Cortisol-Konzentration assoziiert (Artikel V). Außerdem war Technostress signifikant mit Burnout-Symptomen assoziiert in Querschnitt- (Artikel IV), aber nicht in Längsschnitt-Analysen (Artikel V). Insgesamt liefern die Ergebnisse neue Erkenntnisse zu den physiologischen und psychologischen Korrelaten von Arbeitsstress und erste Hinweise auf differenzielle Effekte von Technostress. Weitere prospektive Studien sind erforderlich, um die Ergebnisse zu validieren, die Auswirkungen digitalisierter Arbeitsbedingungen auf die Gesundheit von Beschäftigten weiter aufzuklären und gezielte Maßnahmen für den Arbeits- und Gesundheitsschutz zu entwickeln.

Complete List of Publications

Becker, L., Kaltenegger, H. C., Nowak, D., Rohleder, N., & Weigl, M. (2023). Differences in stress system (re-)activity between single and dual- or multitasking in healthy adults: A systematic review and meta-analysis. *Health Psychology Review*, *17*(1), 78–103. https://doi.org/10.1080/17437199.2022.2071323

Becker, L., Kaltenegger, H. C., Nowak, D., Weigl, M., & Rohleder, N. (2022). Physiological stress in response to multitasking and work interruptions: Study protocol. *PloS One*, *17*(2), e0263785. https://doi.org/10.1371/journal.pone.0263785

Becker, L., Kaltenegger, H. C., Nowak, D., Weigl, M., & Rohleder, N. (2023). Biological stress responses to multitasking and work interruptions: A randomized controlled trial. *Psychoneuroendocrinology*, *156*, 106358. https://doi.org/10.1016/j.psyneuen.2023.106358

Jones, M. T., Kaltenegger, H., Cronin, R. A., & Wright, B. J. (2024). Gender differentiates the predictors of an intention to leave the workplace: a meta-analysis of the effort-reward imbalance workplace stress studies. *Work & Stress*, 1–22. https://doi.org/10.1080/02678373.2024.2364616

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., Quartucci, C., & Weigl, M. (2023). Associations of technostressors at work with burnout symptoms and chronic low-grade inflammation: A cross-sectional analysis in hospital employees. *International Archives of Occupational and Environmental Health*, 1–18. https://doi.org/10.1007/s00420-023-01967-8 *

* This publication is part of the present dissertation

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., & Weigl, M. (2020). Association of working conditions including digital technology use and systemic inflammation among employees: Study protocol for a systematic review. *Systematic Reviews*, *9*(1), 221. https://doi.org/10.1186/s13643-020-01463-x *

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., & Weigl, M. (2021). Associations of working conditions and chronic low-grade inflammation among employees: A systematic review and meta-analysis. *Scandinavian Journal of Work, Environment & Health*, *47*(8), 565–581. https://doi.org/10.5271/sjweh.3982 *

Kaltenegger, H. C., Doering, S., Gillberg, C., Wennberg, P., & Lundström, S. (2021). Low prevalence of risk drinking in adolescents and young adults with autism spectrum problems. *Addictive Behaviors*, *113*, 106671. https://doi.org/10.1016/j.addbeh.2020.106671

Kaltenegger, H. C., Låftman, S. B., & Wennberg, P. (2019). Impulsivity, risk gambling, and heavy episodic drinking among adolescents: A moderator analysis of psychological health. *Addictive Behaviors Reports*, *10*, 100211. https://doi.org/10.1016/j.abrep.2019.100211

Kaltenegger, H. C., Marques, M. D., Becker, L., Rohleder, N., Nowak, D., Wright, B. J., & Weigl, M. (2024). Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation. *Brain, Behavior, and Immunity.* Advance online publication. https://doi.org/10.1016/j.bbi.2024.01.222 *

* This publication is part of the present dissertation

Kaltenegger, H. C., Philips, B., & Wennberg, P. (2020). Autistic traits in mentalization-based treatment for concurrent borderline personality disorder and substance use disorder: Secondary analyses of a randomized controlled feasibility study. *Scandinavian Journal of Psychology*, *61*(3), 416–422. https://doi.org/10.1111/sjop.12595

Kaltenegger, H. C., Weigl, M., Becker, L., Rohleder, N., Nowak, D., & Quartucci, C. (2022). Psychosocial working conditions and chronic low-grade inflammation in geriatric care professionals: A cross-sectional study. *PloS One*, *17*(9), e0274202. https://doi.org/10.1371/journal.pone.0274202 *

* This publication is part of the present dissertation

1. Introduction

1.1 Scientific Background

1.1.1 Stress in the Workplace and its Implications for Health

The relationship between work, working conditions, and health is complex. Work serves important functions for humans beyond earning money (in the case of paid employment): structuring time as well as enabling social contacts, development, status, and identity (Jahoda, 1981; Rau & Hoppe, 2020). However, the workplace can be a source of stress experience and adverse health outcomes. Psychoneuroimmunology and psychoneuroendocrinology have shown that psychological stress can lead to disease, and the biological mechanisms by which stress "gets under the skin" have been well investigated (McEwen, 1998; Miller et al., 2007; Sapolsky, 2018). However, far less is known about the psychophysiological correlates of work stress in particular.

The relationship between work and health is further complicated by global changes such as the digital transformation of work, amplified by the COVID-19 pandemic since 2020 (Frank et al., 2023). For instance, the prevalence of telework in the EU doubled in 2021 to 22% and is expected to further increase due to technological developments as well as employee and employer preferences (Eurofound, 2022). The digitalization of work significantly affects employees' psychosocial working conditions (Dragano & Lunau, 2020). It opens up opportunities, such as increased flexibility in temporal and spatial work organization or automatization of job tasks, while posing risks of stress and mental health problems through the use of digital technologies (Dragano & Lunau, 2020; Rau & Hoppe, 2020). However, the rate of technological development has outpaced research on the physiological and psychological correlates of modern working conditions (Tarafdar et al., 2019).

Stress is a crucial influencing factor for human health and is part of peoples' everyday professional and private life. There is ample empirical evidence on associations of workplace stress with physical and mental morbidity, such as cardiovascular diseases, metabolic conditions, or depression, and mortality (Ferrie et al., 2016; Fransson et al., 2015; Kivimäki et al., 2012; Madsen et al., 2017; Rugulies et al., 2023; Taouk et al., 2020; Watanabe et al., 2018). Work stress models have helped clarify the relationship between psychosocial working conditions and health consequences. For instance, the seminal job demand–control model states that the combination of high job demands and low job control over these demands leads to job strain, and thus, increased risk of disease, particularly cardiovascular (Karasek, 1979; Karasek et al., 1981).

One professional group that deserves special scientific attention in the study of work stress and health implications are healthcare professionals. Being exposed to several work stressors common to other jobs, such as time pressure or organizational issues, but also job-specific stressors related to patient care, healthcare professionals are suggested to be an at-risk population for stress-related physiological perturbations and psychological sequelae such as burnout (Dawe et al., 2016; Maslach, 2003). Moreover, the healthcare system is being fundamentally transformed by health information technology, such as electronic health records or clinical decision support systems, robotic devices, and, most recently, artificial intelligence-based software solutions (Wenderott et al., 2022). The adoption, implementation, and usability of health information technology in clinical care are often insufficient (e.g., Melnick et al., 2020), putting healthcare professionals at increased risk of stress reactions and adverse health outcomes. However, the current evidence base on physiological and psychological correlates of work stress in the age of digitalization in this specific professional group is inconsistent and sparse.

1.1.2 Technostress at Work

Since firstly described by psychologist Craig Brod in the 1980s, the phenomenon *technostress* (Brod, 1982) or *digital stress* (Hefner & Vorderer, 2016; Reinecke et al., 2017; Weinstein & Selman, 2016) has garnered attention by both researchers and the general public. The more frequently used term technostress refers to "stress experienced by end users of Information and Communication Technologies (ICTs)" (Ragu-Nathan et al., 2008, p. 417). Research has identified a number of technology-related factors that can cause technostress, i.e., technostressors (La Torre et al., 2019). Examples are the five technostressors (techno-overload, techno-invasion, techno-complexity, techno-insecurity, techno-uncertainty) introduced by Tarafdar et al. (2007) and work interruptions, multitasking, or information overload due to ICTs (Eppler & Mengis, 2004; Galluch et al., 2015; Hefner & Vorderer, 2016; Reinecke et al., 2017). Technostress has been linked to negative health and performance outcomes among employees (Dragano & Lunau, 2020; La Torre et al., 2019; Riedl, 2012). However, as technostress has mostly been investigated using self-report questionnaires so far, there is a striking lack of studies on objectively measurable physiological effects of technostress.

1.1.3 Physiological Stress Response(s) and Pathways to Disease

According to Sapolsky (2018), "we have a dichotomy—if you're stressed like a normal mammal in an acute physical crisis, the stress response is lifesaving. But if instead you chronically activate the stress response for reasons of psychological stress, your health suffers" (p. 127). In the study of stress and health implications it has proven sensible to differentiate between acute stress reactions and long-term (chronic) stress effects. The acute biological stress response is associated with a series of processes, including activation of the sympathetic nervous system, downregulation of the parasympathetic nervous system, activation of the hypothalamic-pituitary-adrenocortical

(HPA) axis, and complex effects of the immune system with upregulation of some parts, especially inflammatory pathways, and downregulation of others, especially cellular immunity (Chrousos, 2009; Segerstrom & Miller, 2004; Ulrich-Lai & Herman, 2009). In the short term, these adaptations are necessary for survival, yet in the long term, due to chronic over- or underactivity of the stress systems wear and tear effects can occur predisposing the organism to disease, as described in the influential allostatic load model (McEwen, 1998; McEwen & Stellar, 1993).

One key mechanism that explains how chronic stress, like work stress, "gets under the skin" and ultimately leads to disease is the phenomenon of chronic low-grade inflammation (Rohleder, 2019). Systemic inflammatory processes have been shown to be involved in many severe chronic conditions, such as cardiovascular and metabolic diseases or cancer, which are among the leading causes of deaths worldwide (Couzin-Frankel, 2010; WHO, 2022). Inflammation can be measured with a range of biomarkers in the blood, such as the acute-phase-protein C-reactive protein (CRP) or cytokines (see Kaltenegger et al., 2020 for a list). Another important pathway linking stress exposure to disease is the HPA axis with the glucocorticoid cortisol (Miller et al., 2007). Traditionally, cortisol is measured via fluid-based biomarkers, but analysis of cortisol in human hair is increasingly used in psychoneuroendocrinology research as an indicator of chronic stress (Stalder et al., 2017). A better understanding of how working conditions and technostress may affect key mechanisms in pathogenesis (i.e., low-grade inflammation and the HPA axis) is thus crucial to unveil effects on long-term health.

1.1.4 Psychological Health: Associations With Burnout

In addition to their physiological underpinnings, working conditions in the digital age may impair psychological health. In media discourse, digital stress is often portrayed in the context of various negative psychological consequences, such as smartphone and

social media addiction or psychosomatic and cognitive complaints (Kinnebrock & Nitsch, 2020). However, a closer look into the actual evidence base on work-related technostress and mental health shows that empirical studies are scarce and often limited by methodological shortcomings as well as the predominant use of cross-sectional designs (Dragano & Lunau, 2020). First findings suggest an association of technostress(ors) with burnout (Berg-Beckhoff et al., 2017; Dragano & Lunau, 2020), a psychological health outcome widely acknowledged in occupational health science as a potential ramification of chronic work stress (Maslach, 2003; Rohleder, 2018). Burnout can be defined as a combination of exhaustion, mental distance, emotional as well as cognitive impairment, and a series of further symptoms such as depressed mood (Schaufeli et al., 2019). It is a common phenomenon in healthcare workers, harming not only the affected individuals but also the quality of care, patient safety, and the entire healthcare system (Dall'Ora et al., 2020; Weigl, 2022). Hence, more advanced investigations into technostress and burnout in healthcare professionals are needed.

1.2 Present Dissertation

1.2.1 Context and Objective

The present cumulative dissertation was part of a research project on the biomedical consequences of stressors related to the use of digital technologies and media at the workplace (original title: “Biomedizinische Folgen von Belastungen durch digitale Medien und Technologien am Arbeitsplatz”) within the Research Association on Healthy Use of Digital Technologies and Media (“ForDigitHealth”) funded by the Bavarian Ministry of Science and Arts (2019–2023). This interdisciplinary research association consisted of 11 research groups at five universities (Augsburg, Bamberg, Erlangen–

Nuremberg, Munich, and Würzburg) in Bavaria, Germany (for more details on the entire research association, please see André & Rohleder, 2023).

Considering the above outlined knowledge gaps (chapter 1.1), this dissertation sought to contribute to the understanding of effects of (digital) working conditions on employees' physiological and psychological health outcomes in various ways. First, in this work, as a novel approach, the methods of psychobiological stress research (i.e., biomarker measurements) were applied to scrutinize the effects of technostress at work. Second, to better understand long-term health consequences, potential alterations in key biological systems due to chronic stress were investigated in real-world work settings and high-risk populations (i.e., healthcare professionals). Third, in contrast to existing studies with predominantly cross-sectional designs, this work focused on prospective designs to derive conclusions on a higher level of evidence. An in-depth and evidence-based understanding of the physiological and psychological correlates of working conditions in general and technostress in particular is crucial for effective occupational health and safety solutions.

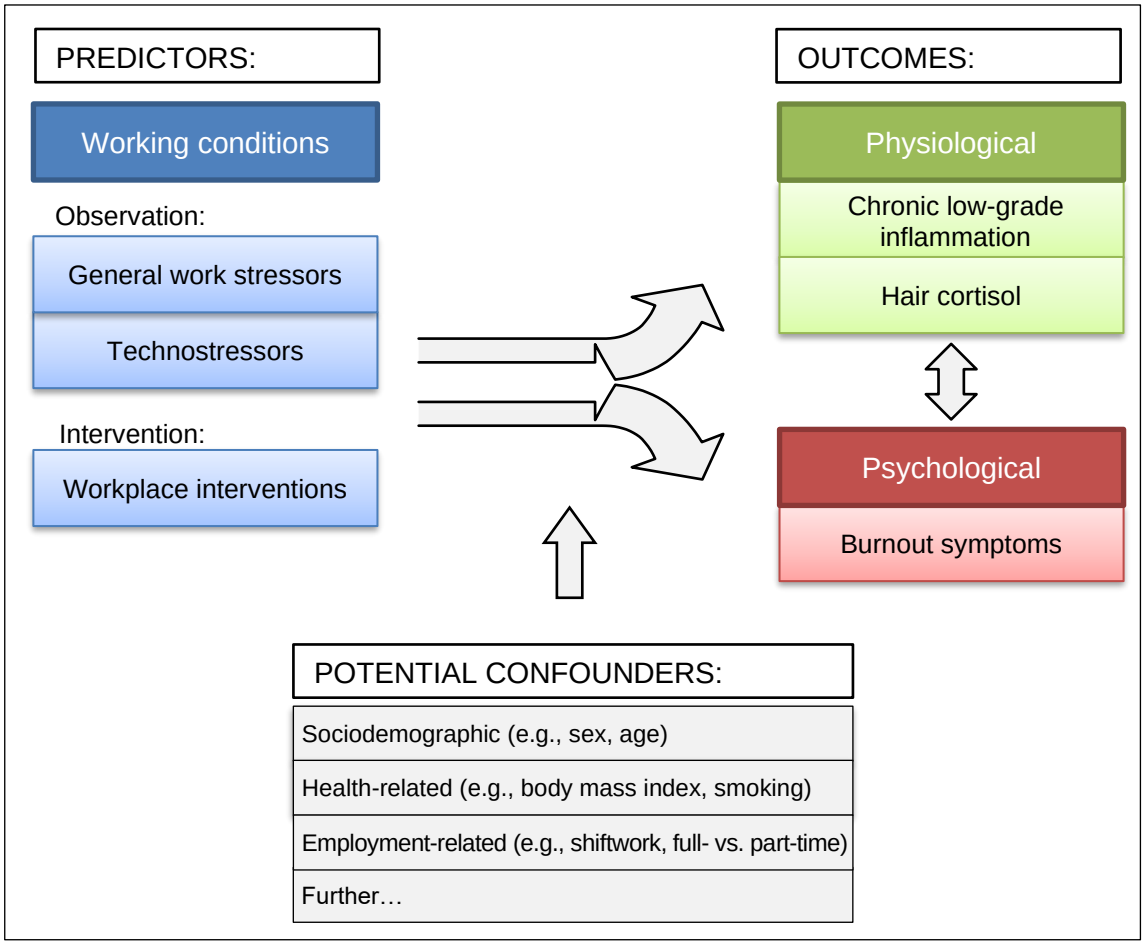
1.2.2 Research Question and Aims

The overarching research question of this cumulative dissertation was whether exposure to technostressors at work—beyond general work stressors—is associated with physiological stress reactions and psychological health sequelae in employees. At the beginning of the research project, a conceptual framework was developed that included the core constructs and associations of interest within this dissertation (**Figure 1**). As illustrated in **Figure 1**, the influence of work-related exposures (predictors) on employees' physiological and psychological outcomes was empirically investigated. As predictors, working conditions, in particular general work stressors, such as job demands or job control, and technostressors, such as work interruptions, multitasking, or

information overload due to ICTs, as well as workplace interventions were assessed. As outcomes, biomarkers of physiological stress responses, particularly of the immune system (i.e., chronic low-grade inflammation) and the HPA axis (i.e., hair cortisol), as well as self-reported psychological health consequences (i.e., burnout symptoms) were examined. In addition, a broad range of relevant, potentially confounding factors, including sociodemographic, health-, and employment-related characteristics, was considered.

Figure 1

Conceptual Framework of the Dissertation Including Main Study Variables and Associations



To analyze potential associations between the depicted constructs, the following aims were determined and empirically investigated step-by-step:

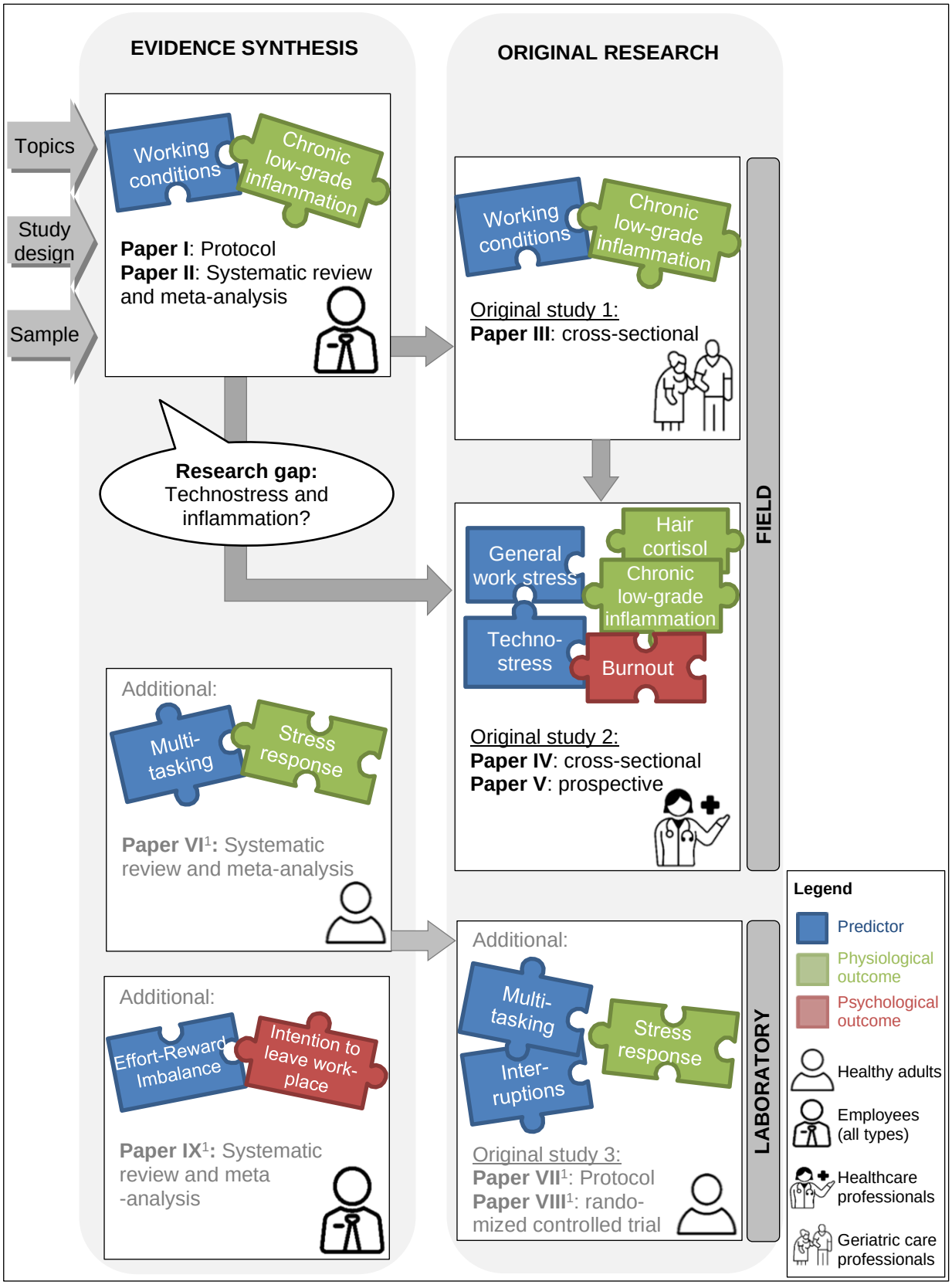
1) to systematically summarize and statistically synthesize the current evidence base on associations between working conditions (and workplace interventions) and chronic low-grade inflammation among employees; and to identify existing studies on associations between technostress(ors) and chronic low-grade inflammation (systematic review and meta-analysis)
2) to assess associations between working conditions and chronic low-grade inflammation in real-world work settings (original studies 1, 2a, & 2b)
3) to investigate associations between technostressors and chronic low-grade inflammation in a real-world work setting (original studies 2a & 2b)
4) to examine associations between technostressors and burnout symptoms in a real-world work setting (original studies 2a & 2b)
5) to explore associations between technostressors and hair cortisol as well as associations between low-grade inflammation, hair cortisol, and burnout symptoms in a real-world work setting (original study 2b)
6) to identify implications for future research as well as for occupational health and safety practice (systematic review and meta-analysis; original studies 1, 2a, & 2b)

1.2.3 Methods

To conduct a thorough and comprehensive investigation of the overall research question and to implement the above stated aims (chapter 1.2.2), a combination of evidence synthesis (i.e., systematic reviews with meta-analyses) and original research in the field (and laboratory) was selected. **Figure 2** shows a flow diagram of this two-stage research process including the investigated research topics and samples as well as utilized study designs.

Figure 2

Flow Diagram of the Research Process Including Topics, Study Designs, and Samples



Note. [1] Paper is not part of this dissertation.
(Source: author's illustration, created with Canva)

As a first step and in line with aim 1), a protocol for a systematic review and meta-analysis was developed to investigate associations between working conditions and chronic low-grade inflammation in all types of employees (Paper I). Based on this protocol, a systematic review with meta-analysis (Paper II) was performed. With a total of 23 identified eligible studies, it showed that the current research base on this topic was limited and that there was a gap in research on work-related technology use and inflammatory responses.

Concurrent with the review and building upon the collated knowledge, original study 1 was conducted to realize aim 2). Based on the data of a prior investigation of geriatric care professionals (Chmelar et al., 2017), this cross-sectional study assessed associations between self-reported psychosocial working conditions and biomarkers of chronic low-grade inflammation in a real-world work setting (Paper III). As a next step, original study 2, a large-scale prospective cohort study, was designed and conducted to address the identified research gap. After the development of a study protocol (registered at https://osf.io/r5ced) and approval by the Ethics Committee at the Medical Faculty of Ludwig Maximilian University of Munich (20–0914), data were collected over three study waves (i.e., at baseline, after 6 months, and after 12 months). To gain insights into potential causal relations of working conditions with physiological and psychological correlates, a full panel design was used, meaning that both predictors and outcomes are measured in each wave (Taris & Kompier, 2014). Like original study 1, this study was conducted in healthcare workers, a population at risk for work-related stress in general and technostress in particular (see chapters 1.1.1 and 1.1.4). A cohort of new employees at a large university hospital in South Germany was recruited and followed up for over one year. Standardized questionnaires for self-report and biomarker measurements (i.e., high-sensitivity C-reactive protein [hs-CRP], hair cortisol) were combined. For a profound investigation of study objectives 2–4, both cross-sectional (Papers III & IV) and

prospective analyses (Paper V) were performed; for objective 5, only prospective analyses were conducted (Paper V).

This research project featured several collaborations. In addition to chronic effects, the focus of this doctoral thesis, acute physiological stress responses to prominent technostressors (i.e., multitasking and work interruptions) were explored (principal investigator: Prof. Dr. Nicolas Rohleder; Prof. Dr. Linda Becker). In a systematic review and meta-analysis (Paper VI: Becker, Kaltenegger, Nowak, Rohleder, & Weigl, 2023), differences in the (re-)activity of the physiological stress systems between single- and multitasking were investigated. Drawing upon the collected evidence and aiming to close the identified research gaps, original study 3, a randomized controlled trial in the laboratory, was developed (Paper VII: Becker et al., 2022) and conducted among healthy adults (Paper VIII: Becker, Kaltenegger, Nowak, Weigl, & Rohleder, 2023).

Moreover, in a further collaborative project (principal investigator: Prof. Dr. Bradley Wright) another systematic review with meta-analysis (Paper IX: Jones et al., 2024) was performed on effort-reward imbalance (Siegrist, 1996), a well-established model on work stress, and intention to leave the workplace, a critical outcome among healthcare professionals worldwide (e.g. Burmeister et al., 2019).

2. Publications of the Dissertation

This cumulative dissertation comprises a compilation of five scientific articles (see Table 1, for an overview).

Table 1

Overview of Papers Included in the Present Dissertation

Paper	Study Type	Title	Journal	Impact & Ranking: JIF; JIF Percentile (category/ categories) in year of publication	Page
I	Protocol	Association of working conditions including digital technology use and systemic inflammation among employees: Study protocol for a systematic review	*BMC Systematic Reviews*	2.52; 57.19 (Medicine, General & Internal–SCIE) in 2020	23
II	Systematic review and meta-analysis	Associations of working conditions and chronic low-grade inflammation among employees: A systematic review and meta-analysis	*Scandinavian Journal of Work, Environment & Health*	5.49; 75.48/ 84.34 (Public, Environmental & Occupational Health–SCIE/ SSCI) in 2021	35
III	Original study 1	Psychosocial working conditions and chronic low-grade inflammation in geriatric care professionals: A cross-sectional study	*PloS One*	3.7; 65.1 (Multidisciplinary Sciences–SCIE) in 2022	54
IV	Original study 2a	Associations of technostressors at work with burnout symptoms and chronic low-grade inflammation: A cross-sectional analysis in hospital employees	*International Archives of Occupational and Environmental Health*	3.0; 45.2 (Public, Environmental & Occupational Health–SCIE) in 2022 [1]	72
V	Original study 2b	Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation	*Brain, Behavior, and Immunity*	15.1; 94.1 (Immunology–SCIE) 96.5 (Psychiatry–SCIE) 97.2 (Neurosciences–SCIE) in 2022 [1]	91

Note. JIF = Journal Impact Factor; SCIE = Science Citation Index Expanded; SSCI = Social Sciences Citation Index.

[1] most recent metrics (metrics for the years 2023 and 2024 not available yet).

2.1 Paper I

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., & Weigl, M. (2020). Association of working conditions including digital technology use and systemic inflammation among employees: Study protocol for a systematic review. *Systematic Reviews*, *9*(1), 221. https://doi.org/10.1186/s13643-020-01463-x

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Systematic Reviews

PROTOCOL Open Access

Association of working conditions including digital technology use and systemic inflammation among employees: study protocol for a systematic review

Helena C. Kaltenegger[1*], Linda Becker[2], Nicolas Rohleder[2], Dennis Nowak[1] and Matthias Weigl[1]

Abstract

Background: With the dynamic advancement of digitalization, working environments are changing and risk for employee stress may be increasing. Work stress has been associated with a dysregulation of inflammatory processes as a component of immune function. Systemic low-grade inflammation is discussed as a key player in the relation between stress exposure and chronic illness, such as cardiovascular diseases. The objective of this investigation will be to evaluate the association of working conditions including digital technology use and systemic inflammation among employees.

Methods: We designed and registered a study protocol for a systematic review of randomized controlled trials and prospective non-randomized studies (e.g., cohort, interrupted time series, or before-after studies). We will include studies conducted among adult workers reporting associations of working conditions and inflammatory activity. The outcome will be biomarkers of systemic low-grade inflammation on cell, plasma molecule and intracellular level, such as C-reactive protein, or different types of leukocytes, cytokines, etc. Literature searches will be conducted in several electronic databases (from January 1982 onwards), including PubMed/MEDLINE, Embase, PsycINFO, Web of Science, and CENTRAL. Two reviewers will independently screen all retrieved records, full-text articles, and extract data. The study methodological quality (or bias) will be appraised using appropriate tools. Our results will be described qualitatively. Random effects meta-analysis will be conducted, if feasible and appropriate. Additional analyses will be performed to explore potential sources of heterogeneity.

Discussion: This systematic review and meta-analysis will provide a synthesis of studies evaluating the association of working conditions and systemic inflammation. We anticipate our findings to identify knowledge gaps in the literature that future research should address. Moreover, results of our review may provide implications for corporate and public policy action for employee health promotion and prevention of occupational stress.

Systematic review registration: PROSPERO ID: CRD42020166887

Keywords: Work, Job, Health, Working conditions, Occupational stress, Digitalization, Technostress, Inflammation, Inflammatory markers, Immune system

* Correspondence: helena.kaltenegger@med.uni-muenchen.de
[1]Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, Ludwig-Maximilians-University of Munich, Ziemssenstraße 1, 80336 München, Germany
Full list of author information is available at the end of the article

Background

In the light of contemporary and profound changes in the world of work coined by digitalization, the workplace may represent a significant cause of stress, and employee health promotion becomes increasingly important. Exposure to work stress has been associated with physical and mental ill health, such as cardiovascular diseases, type 2 diabetes, and clinical depression, as well as mortality [1–6]. With the dynamic advance of technologization and digitalization in humans' workplaces and private lives, stress experience related to the interaction with information (and communication) technologies and systems has become a phenomenon of rapidly growing scholarly interest. Research on *technostress* [7] and *digital stress* [8–11] has identified a broad range of potential sources of stress, such as techno-invasion, interruptions, information overload, complexity, invasion of privacy, etc. [12–15], and moreover, has revealed effects on the endocrine system with possible implications for immune function [16].

Sustained low-grade inflammation as a sub-component of the immune system is discussed as a central process in the association between stress exposure and severe long-term diseases [17–20]. Inflammation is mostly assessed by measuring levels of inflammatory markers in plasma or serum, including (proinflammatory) cytokines, such as interleukins (IL; mainly IL-1 (β) and IL-6), tumor necrosis factors (TNF; mainly TNF-α), interferons (IFN), and the acute-phase protein C-reactive protein (CRP) [21–23]. Several studies have shown associations between adverse working conditions, such as high effort-reward imbalance [24], organizational injustice or shift work, and inflammatory activity [25–27]. Reviews and meta-analyses indicate substantial evidence for the relation of acute and chronic psychosocial stress with immune function and inflammatory processes [17, 21, 28, 29]. However, there is a paucity of reviews and meta-analyses examining systemic inflammatory processes due to working conditions and/or work-related stress. Previous reviews and meta-analyses have focused on associations between workplace stress and immune function [30, 31], and on work-related psychosocial factors and inflammatory markers [32]. However, to our knowledge, there are no systematic reviews and meta-analyses investigating the strength of the evidence on the prospective association of various modern working conditions including digital technology use and employees' systemic inflammatory markers.

We plan to conduct a systematic review on the association of working conditions including digital technology use and systemic inflammation among employees. There are two aims within the planned review: The first aim will be to determine the current evidence on associations between working conditions and inflammation based on randomized controlled trials and prospective non-randomized studies and to assess if different classes of working conditions are differently associated with inflammatory markers. The second aim will be to identify if there are studies specifically investigating work-related use of digital technologies and inflammatory markers, and if so, evaluate their potential associations.

Methods

Protocol registration and reporting information

The present protocol has been registered within the PROSPERO database (registration ID: CRD42020166887). This protocol is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement [33, 34] (see PRISMA-P checklist in Additional file 1). The proposed systematic review will be reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [35, 36]. Information on roles, responsibilities, and skills of review team members is provided in Additional file 2.

Eligibility criteria

Studies will be selected according to the following study characteristics: study design, participants, exposure/interventions, comparators, outcomes (PECO/PICO framework):

- *Study design*: Eligible studies will be prospective field studies reporting associations between working conditions and systemic inflammation. We will include observational and interventional studies, i.e., randomized controlled trials and non-randomized studies of interventions, such as controlled before-and-after studies or interrupted time series designs. There will be no restrictions by type of occupational setting. Laboratory studies will be excluded.
- *Participants:* We will include all types of adult workers and employee samples. We will consider all types of occupations, such as managers, professionals, technicians and associate professionals, clerical support workers, services and sales workers, agricultural workers, craft and related trades workers, plant and machine operators and assemblers, and elementary occupations (see [37]); as well as sectors, such as agriculture/forestry, chemical industries, commerce, construction, education, engineering, financial services, health services, transport, etc. (see [38]). Unemployed individuals, students, athletes, artists, military personnel, and clinical samples based on specific diagnoses will be excluded.
- *Exposures/interventions*: Studies assessing all kinds of working conditions will be eligible, encompassing a

broad range of work- and employment-related aspects, like working time, compensation, mental and physical demands [39]. We will include studies examining all kinds of psychosocial factors at work, such as work environment, job content, and organizational conditions [40]. Moreover, studies focusing on work-related use of digital technologies and media as well as associated stressors, such as techno-overload or interruptions [15, 41], will be included. We define digital technologies as the entirety of all electronic devices (hardware) and applications (software) that use information based on number codes, and the entirety of all media coded in formats that can be processed by these devices and applications. Work-related digital technologies may comprise computers, e-mails, mobile phones, internet, messaging systems, artificial intelligence, autonomous systems, robots, virtual reality, etc. Studies examining specific environmental hazards, i.e., chemical or physical agents in the air, water, soil, food, or extreme heat, will be excluded. We will exclude studies assessing shiftwork (for a review, see, e.g., [42]) and socioeconomic status as exposure variables. Studies investigating all kinds of workplace-related interventions, that is, all measures directly or indirectly aiming at occupational health promotion (on or off site), will be eligible. We will exclude studies on nutraceutical interventions.

- *Comparators:* If applicable, the comparator group will be based on subjects not exposed to a specific working condition/exposed to a lesser extent or not exposed to a specific workplace intervention/ exposed to a different intervention.
- *Outcomes*: Our outcome of interest will be changes in markers of systemic low-grade inflammation measured in the blood or saliva. We will consider three main categories of indicators of systemic inflammation: cells, plasma molecules, and intracellular processes. Regarding cells, we will include studies examining leukocytes (and subtypes) and dendritic cells. With regard to plasma molecules, we will include studies on the acute-phase proteins CRP, fibrinogen, and serum amyloid A, and on cytokines including different chemokines, interleukins, lymphokines, and monokines as well as IFN-γ and TNF-α. Cell-free DNA, inflammasomes, and intercellular adhesion molecule-1 will also be included as target outcomes. Concerning intracellular processes, we will include studies on the transcription factors AP-1, NF-IL6, and NF-kappa B, and on gene expression associated with inflammatory processes (see Table 1 for a list of included markers). We will exclude studies assessing inflammatory markers as indicators of organ damage, such as kidney injury. All inflammatory markers will be considered as main outcomes; there will be no prioritization or secondary outcomes. We will include studies with at least one follow-up measure, i.e., two consecutive measurements, of outcome variables.

We will include studies published from January 1982 (considering the introduction of the term *technostress* [7] in 1982) onwards. We will include articles in peer-reviewed journals reported in the languages English and German. A list of possibly relevant titles in other languages will be provided in the final study report as an appendix. We will exclude conference proceedings, dissertations, or theses.

Information sources and search strategy

The primary source of relevant literature will be a structured search using several electronic databases (from 1982 onwards): PubMed/MEDLINE, Embase, PsycINFO, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). The secondary source of potentially relevant material will be a search for the difficult to locate literature, including Google Scholar. We will perform hand searching of reference lists of included studies and relevant reviews to identify additional eligible papers. Experts and prolific authors in the field will be contacted and consulted. The literature searches will be designed and conducted by the review team. The search will include a broad range of terms and keywords related to the PECO/PICO question (e.g., “worker”, “job control”, “social support”, “communication technology”, “digital stress”, “inflammation”, “immune system”). A full draft of the search strategy for PubMed/MEDLINE is provided in Additional file 3. This search strategy will be adapted to the other databases using the software Systematic Review Accelerator [43].

Screening and selection procedure

All retrieved titles and abstracts of identified articles will be imported into the software *EndNote* X8 (Thomson Reuters). The screening process will be conducted using the web and mobile application Rayyan [44]. Two independent reviewers (HK, MW) will conduct a systematic and stepwise selection of eligible studies, that is, screening of titles, abstracts, and full texts. Reviewers will discuss potential discrepancies until a consensus is reached. Potential conflicts between the two reviewers will be resolved after the consultation of a third reviewer (LB) from the study team. Excluded studies will be recorded. All steps of the study selection will be tested prior, in order to identify potential misunderstandings between the reviewers regarding the eligibility criteria or the software interface. This pre-test will include a random sample of 20 records. A flow diagram presenting the study selection process will be prepared [35].

Table 1 Outcome category, definition, and included inflammatory markers per category

Outcome category	Definition of outcome category	Inflammatory markers (per outcome category)
Cells	Inflammation-related processes on cell level as a component of cellular immunity	Leukocytes Eosinophils Granulocytes Lymphocytes Macrophages Monocytes Neutrophils Dendritic cells
Plasma molecules	Inflammation-related processes on plasma protein level as a component of humoral immunity	Acute-phase proteins C-reactive protein (CRP) Fibrinogen Serum amyloid A
		Cytokines Chemokines Interferon-gamma (IFN-γ) Interleukins (IL) Lymphokines Monokines Tumor necrosis factor-alpha (TNF-α)
		Cell-free DNA
		Inflammasomes
		Intercellular adhesion molecule-1
Intracellular processes	Inflammation-related processes on intracellular level	Transcription factors AP-1 NF-IL6 NF-kappa B Gene expression Transcripts for proteins associated with inflammatory processes Transcriptomics focusing on or revealing inflammatory processes

Data collection process

Data will be extracted independently by two authors (HK, MW) and imported into *Excel* (Microsoft Office Professional Plus, 2016). This step will be pre-tested with five articles to test for feasibility and comprehensiveness. A third reviewer (NR) from the study team will be included as a consultant in case of disagreement. Several main categories and individual data will be extracted from all eligible articles (see Table 2). In the case of missing information, corresponding authors will be contacted to obtain information relevant to this review. If there are multiple reports of a single study, only the key paper will be included (authors will be contacted, if not clear).

Data processing and classification of exposure and outcome variables

With regard to the exposure variables, two reviewers (HK, MW) will perform a criteria-based classification of working conditions according to the scheme presented in Fig. 1. First, included studies will be categorized concerning their underlying theoretical model. Working conditions will be classified into job demands and resources as main categories with respective subcategories based on the following four models:

- *Job demand-control model* (JDC [45]): The JDC model postulates that mental strain in a workplace context results from the combination of the two dimensions job demands and job control. High job demands, such as time pressure or workload, and low decision latitude are associated with mental strain and job dissatisfaction.
- *Job demand-control-support model* (JDCS [46, 47]): This model is an extension of the JDC model by integrating the dimension social support.
- *Job demands-resources model* (JDR [48]): The JDR model suggests that high job demands lead to strain and health impairment, whereas high resources lead to increased motivation and productivity [49]. In the long-term, an interaction between extreme job demands, which lead to exhaustion and a lack of resources leading to disengagement from work, can result in the development of burnout [48].
- *Challenge-hindrance stress model* (C-H [50]). The C-H stress model proposes that work stressors can be divided into two categories (challenge vs. hindrance stressors), which are differently associated (positively vs. negatively) with work outcomes (see [51, 52]). In the primary investigation, challenge stressors—related to the phenomenon of eustress—were shown to be positively associated with job satisfaction and

Table 2 Main categories and data extracted from included articles

Main categories		Data to be extracted
I	Study characteristics	- Authors and year of publication
		- Study design
		- Country of study
		- Period of follow-up and follow-up rate
		- Occupational setting
II	Samples	- Participants: demographics, professional characteristics, health-related variables
		- Sample size
III	Type and assessment of exposures/interventions and comparators	- Type of working condition (e.g., job demands, job control, workload, social support, digital technology use)
		- Type of workplace intervention (e.g., physical activity, stress reduction)
		- Type of comparator
		- Methods of assessment
IV	Type and assessment of outcomes	- Category and type of inflammatory markers
		- Source of outcomes (blood, saliva)
		- Method/technique of assessment
V	Statistical analyses and reported results	- Type of statistical methods and analyses
		- Means and variance metrics of inflammatory markers (e.g., standard deviation, confidence intervals)
		- Coefficients (β, γ) and/or measures of strength of associations between working conditions and inflammatory markers (OR, RR, HR with SE, and/or 95% CI)
		- Effect sizes (if reported or calculable)
		- *P* -values
VI	Moderators/control of confounders	- Potential moderator or confounder variables or analyses (if reported)
		- Results of respective analyses (if reported)
VII	Further study information	- Further information of potential interest (e.g., limitations, restrictions to validity)

negatively with job search, in contrast to distress evoking hindrance stressors found to be oppositely associated with these outcomes [50].

We are aware that hybrid models do exist in this context, such as the differentiated JDR model [53, 54], and we will classify studies accordingly, i.e., multiple allocations are possible. With regards to the category "resources", in line with the JDR model [48], we will focus on external resources since they are more likely to be subjected to job design approaches in contrast to rather stable internal resources, such as cognitive features (see [55]); we will further distinguish between control, task-related, organizational, and social resources. If working conditions in eligible publications are reported without an underlying model, these studies will be assigned to a residual category. In addition, we will conduct a feature-based classification of every study concerning specific characteristics of the work situation irrespective of the underlying model. First, we will identify if working conditions involve digital technology use or not (as defined above). Second, we will distinguish between mental vs. non-mental, i.e., intellectual vs. physical, working conditions. Third, we will consider the time frame of working conditions, i.e., we will differentiate between acute and chronic (provided by author definition) working conditions (see Fig. 1).

Risk of bias in individual studies

To evaluate the methodological quality of all eligible studies as well as potential limitations to validity, a standardized risk of bias assessment will be performed. Since this review will include investigations using different study designs, three different established tools to assess the risk of bias will be applied by two independent reviewers (HK, MW). (1) For randomized controlled trials, the *Cochrane Risk of Bias Tool* (RoB 2 [56]) will be used. (2) For non-randomized studies of interventions, the *Risk Of Bias In Non-randomized Studies – of Interventions* (ROBINS-I [57, 58]) tool will be utilized. These two risk of bias assessment tools include sets of questions addressing different domains of potential sources of bias from selection to reporting, and to be answered with proposed judgements. (3) For prospective observational studies, the checklist *Quality of Reporting of Observational Longitudinal Research* [59] will be applied. In

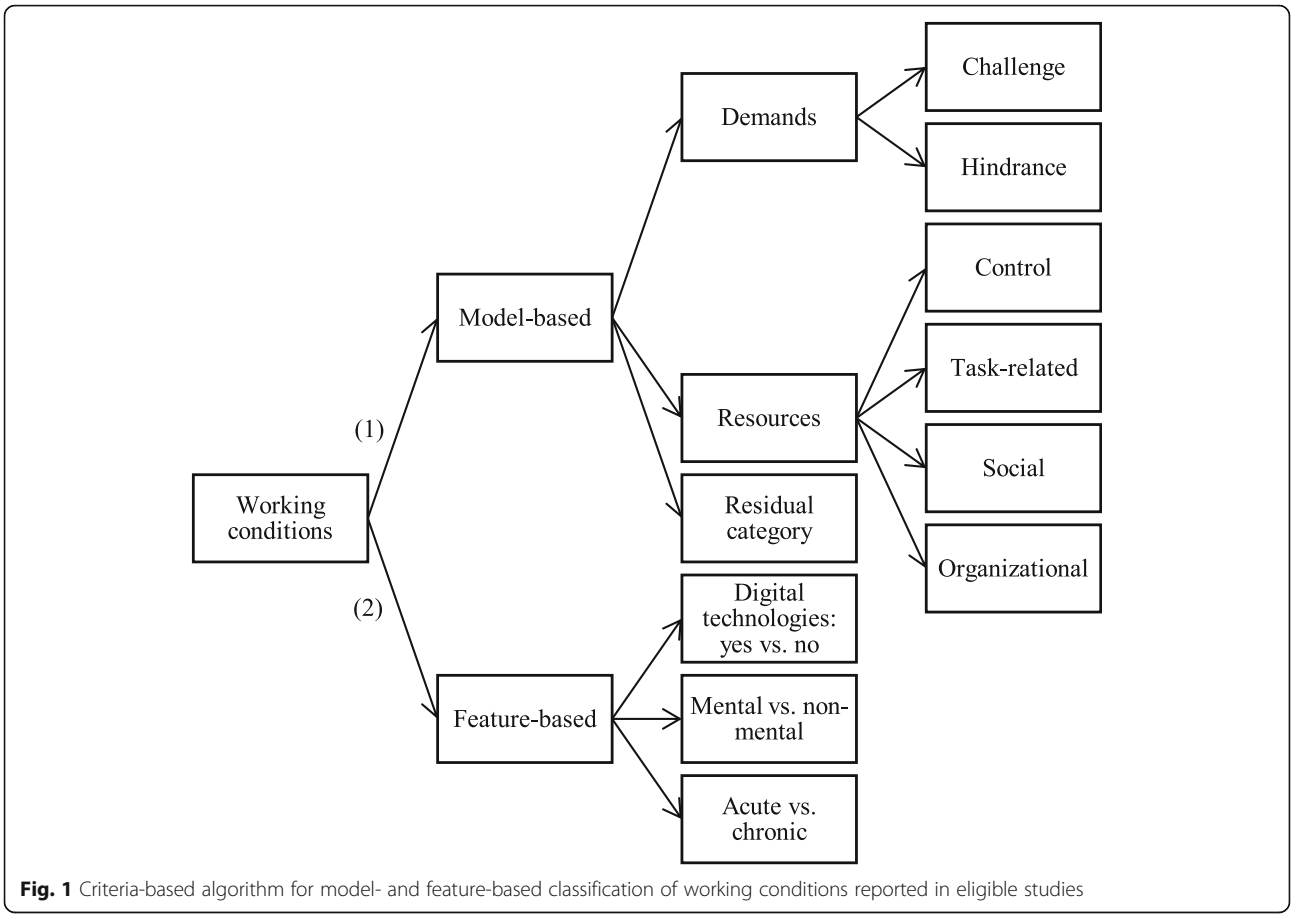

Fig. 1 Criteria-based algorithm for model- and feature-based classification of working conditions reported in eligible studies

case of disagreement between both reviewers, a third reviewer (LB) from the study team will be consulted and act as a tiebreaker to obtain a final evaluation. Our risk of bias assessment will be pre-tested using a sample of five, randomly selected articles of each study design category (see above). This step will ensure a joint understanding and application of the risk of bias evaluation tools between all reviewers.

Data synthesis

First, we will provide a qualitative summary of the information extracted from each included study and of our risk of bias assessment in narrative and tabular form. In case of substantial heterogeneity and inappropriateness of statistical pooling, we will apply graphical summary approaches for evidence synthesis in the absence of meta-analysis, i.e., harvest plots, effect directions, or bubble plots for summarizing information in an accessible and user-friendly manner (see [60]).

Secondly, if a sufficient number of high-quality studies with a relatively low level of heterogeneity is retrieved, we will quantitatively synthesize data from primary studies in a meta-analysis, using *R* 3.5.2 (package: *metafor* [61]). Due to anticipated heterogeneity of effects in individual studies, we will select a random effects model based on the DerSimonian and Laird [62] method, in order to estimate the average of the effects across studies. Heterogeneity will be assessed by estimating the variance between primary studies using Cochran's *Q* test [63] and I^2 statistic [64]. Results will be illustrated graphically using forest plots including individual study effects (step 1) and combined effect estimates (step 2) as well as confidence intervals, respectively [65].

Additional analyses

If the number of identified studies allows for, potential sources of heterogeneity will be explored further by subgroup analyses or meta-regression based on PECO/PICO and study design characteristics [66, 67]. We intend to perform subgroup analyses for potential effect modifications by age (e.g., young vs. middle-aged vs. elderly professionals) and sex (men vs. women), as age and sex are important determinants in work-related stress level, yet with inconsistent effects reported in the literature [68, 69]. Moreover, we plan to group studies regarding the type of exposure according to our criteria-based classification of working conditions (model based: demands vs. resources; feature based: digital vs. non-digital, mental

vs. non-mental, acute vs. chronic). We will distinguish between observational and interventional study designs, and if enough studies will be identified, we intend to provide post hoc classifications regarding workplace interventions (e.g., organizational/structural vs. individual/behavioral). In case a sufficient set of studies with a large variety of outcomes is retrieved, subgroup analyses based on our defined outcome categories (i.e., cells, plasma molecules, intracellular processes; see Table 1) will be undertaken. Finally, we plan to conduct sensitivity analyses to test for effects of exclusion of particular studies on the results based on methodological quality according to the risk of bias assessment and measurement/source of inflammatory markers (i.e., exclusion of studies using salivary markers) [67].

Meta-biases

The results of the review and meta-analysis will be critically examined with respect to sources of meta-bias, such as selective reporting within studies or publication bias across studies. We plan to generate a funnel plot, and tests for asymmetry (e.g., Egger's test [70]) including at least 10 studies (if possible) will be performed to check for small-study effects [67, 71, 72]. Furthermore, we will apply the critical appraisal tool for systematic reviews on randomized and/or non-randomized studies of healthcare interventions AMSTAR-2 [73].

Confidence in cumulative evidence

The strength of the body of evidence will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE), a system for rating quality of evidence and strength of recommendations [74, 75]. Quality of evidence refers to the confidence that the estimates of the effect are correct and can be classified in one of four levels—high ("further research is very unlikely to change our confidence in the estimate of effect"), moderate ("further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"), low ("further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"), and very low ("any estimate of effect is very uncertain") [74, 76]. Threats to quality of evidence comprise study limitations, inconsistency of results, indirectness of evidence, imprecision as well as publication bias, and quality rating can be downgraded by the presence of these five factors [77]. The strength of recommendation is defined as the confidence that the desirable effects of an intervention outweigh its undesirable effects and can be graded as strong or weak [74, 78]. GRADE has been successfully used in the fields of clinical medicine, public health, and policy making, and more recently, its application has been advanced to studies in occupational and environmental health [79, 80].

Discussion

This protocol describes the methodology for a systematic review of the current study base on the association between working conditions including digital technology use and inflammatory markers in employees. We propose a rigorous assessment and synthesis of the current literature base with particular focus to high-quality studies, potentially allowing for evidence-based inferences concerning the actual state of knowledge on employees' inflammatory level that can be attributed to working conditions and job environment.

The protocol specifies all necessary steps of our systematic review limiting any potential bias that may occur a posteriori. It includes well-defined criteria for searching the scientific literature, study selection, risk of bias assessment, data extraction, and synthesis of findings. However, we are aware of potential sources of bias that may exist a priori and are foreseeable. Since our search does not include unpublished data and gray literature, we acknowledge that selection bias in terms of publication bias may occur. Moreover, language bias may be introduced by restrictions of eligible publications to English and German language. Although we cannot exclude that relevant studies have been conducted and/or published in other languages, we are confident that the validity and precision of our findings will not be substantially affected by language bias. Previous research suggests that restrictions beyond the English language introduce little to no systematic bias [81–83].

In the light of the limitations of previous and current research attempts [30–32], our investigation aims at advancing knowledge on the association of working conditions and systemic inflammation among employees particularly by three contributions: (1) We will only incorporate prospective studies to draw our effect estimates upon on a study base with high level of evidence designs. (2) A criteria-based classification of working conditions based on prominent job stress models will be provided, and digital technology use will be considered as a particular type of exposure. (3) Our review will include a comprehensive set of inflammatory markers, encompassing phenomena on different molecular biological levels (i.e., cells, plasma molecules, intracellular processes) and taking into account recent advancements in stress biomarker research, such as cell-free DNA. This broader scope expands the set of potential markers that indicate dysregulation of inflammatory processes associated with working conditions and will allow inferences concerning the feasibility and utility of bio-psychological markers for the assessment of employees' inflammation level in occupational contexts.

Difficulties in the procedure of our planned review could relate to the retrieval of a large amount of records not relevant to our research question, due to the extensive set of search terms. An important challenge might be the rigorous and consistent exclusion of non-eligible studies according to our PECO/PICO characteristics. For instance, we anticipate that many of the retrieved studies include samples with previous medical conditions, such as cardiovascular diseases, or address inflammation as an acute clinical condition (e.g., in connection with injury) rather than chronic subclinical inflammation. Any amendments made to the protocol will be depicted and documented in the final publication of the review. The completed review is intended to be published in a peer-reviewed journal in the field of occupational medicine or work psychology and will be presented at scientific conferences and other scientific outlets.

Several limitations of our anticipated investigation have to be considered on individual study and review level. Although our classification of working conditions is based on well-established occupational stress models, the selection may be regarded as arbitrary since other theories and models of great importance do exist in this field (e.g., effort-reward imbalance model [24]). Moreover, the validity and key propositions of the included models remain subject to scientific scrutiny: While considerable support for additive effects of job demands, job control and social support on psychological well-being ("strain hypothesis", "iso-strain hypothesis") has been found, evidence on moderating effects of job control or social support ("buffer hypothesis") is less consistent, and support in longitudinal compared with cross-sectional studies appears to be weaker [84, 85]. Concerning the C-H model, negative associations with key variables, such as psychological strains or physical health, have been demonstrated for both types of stressors in a recent meta-analysis, confining applicability of the model to few outcomes and questioning the alleged beneficial role of challenge stressors [86]. Nevertheless, keeping these limitations in mind, we assume that our suggested algorithm provides a sensible and feasible categorization of all sorts of studied working conditions. With regard to digital working conditions, we acknowledge that possible applications of digital technologies are multimodal and workplace settings significantly differ in their utilization of tools and modes of digital communication and information technologies, what may limit comparisons across professional settings and samples [87]. Furthermore, we anticipate potential limitations concerning the validity of the outcome inflammation. The selection of inflammatory markers often depends on aspects of measurability and feasibility rather than their pure indicative value for inflammation. Hence, we expect to detect a large body of research on CRP measurements, but, at the same time, we aim to capture other useful parameters of chronic low-grade inflammation by including a broad range of markers previously identified in stress research in our search strategy. With respect to the assessment method of inflammatory markers, we are aware of potential confinements regarding salivary markers (see [17, 88]) and we will consider the assessment method in the data analysis (see above). In addition, inflammation involves a complex interplay of biological processes and should not be assessed in isolation underlining the necessity of adjusting for other variables, such as general health, including physical and mental health conditions associated with inflammation as well as anthropometric parameters, most importantly body fat percentage (or BMI, WHR, etc.). Lastly, the generalizability of the findings of our review will be limited to the working population.

Given the increasing interest and need for knowledge on the effects of modern working conditions on employee health and well-being, we regard our research question as highly relevant. Although we are aware of the difficulties concerning the feasibility of studies with rigor designs and high-level methodology in occupational settings (i.e., randomized controlled trials), we assume that our review results will inform future research in this field in several ways. First, our findings will reveal recommendations for the conductance of high-level investigations in occupational practice settings. Second, the findings will provide guidance for future studies on approaches to improve working conditions with the objective to promote employee health and well-being. Third, this review may help to identify research gaps concerning the effects of specific, but important working conditions, such as those shaped by recent societal developments. Eventually, as a practical implication, collated evidence on the effects of workplace interventions on systemic inflammation may yield indications for corporate and public policy action on employee health promotion.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13643-020-01463-x.

Additional file 1. PRISMA-P checklist (file format: pdf)

Additional file 2. Review team roles and responsibilities (file format: pdf)

Additional file 3. Search strategy for PubMed/MEDLINE (file format: pdf)

Abbreviations

IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; CRP: C-reactive protein; AP-1: Activator protein 1; NF-IL6: Nuclear factor for interleukin-6 expression; NF-kappa B: Nuclear factor "kappa-light-chain-enhancer" of activated B cells; JDC: Job demand-control model; JDCS: Job demand-control-support model; JDR: Job demands-resources model; C-H: Challenge-hindrance stress model; BMI: Body mass index; WHR: Waist-to-hip ratio

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Authors' contributions
HK, MW, LB, NR, and DN contributed to the conception and design of the review; HK developed the search strategy and wrote the first draft of the manuscript; MW, LB, and NR wrote sections of the protocol. All authors contributed to manuscript revision, read and approved the submitted version. MW is the guarantor of the review.

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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

Author details
[1]Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, Ludwig-Maximilians-University of Munich, Ziemssenstraße 1, 80336 München, Germany. [2]Chair of Health Psychology, Institute of Psychology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany.

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2.2 Paper II

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Associations of working conditions and chronic low-grade inflammation among employees: a systematic review and meta-analysis

by Kaltenegger HC, Becker L, Rohleder N, Nowak D, Weigl M

This is the first systematic review and meta-analysis on associations of working conditions and chronic low-grade inflammation solely based on prospective studies. It finds that workplace physical activity interventions were effective in reducing employees' inflammation. However, the current research base is limited and heterogeneous, highlighting the need for prospective studies to advance knowledge regarding pathways from work stress to ill-health.

Affiliation: Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstraße 1, 80336, München, Germany. helena.kaltenegger@med.uni-muenchen.de

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Key terms: chronic low-grade inflammation; employee; health; immune system; inflammation; inflammation; inflammatory biomarker; information and communication technology; job; meta-analysis; occupational stress; systematic review; work; working condition

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Associations of working conditions and chronic low-grade inflammation among employees: a systematic review and meta-analysis

by Helena C Kaltenegger, MSc,[1] Linda Becker, PhD,[2] Nicolas Rohleder, PhD,[2] Dennis Nowak, MD,[1] Matthias Weigl, PhD [1, 3]

Kaltenegger, HC, Becker L, Rohleder N, Nowak D, Weigl M. Associations of working conditions and chronic low-grade inflammation among employees: a systematic review and meta-analysis. *Scand J Work Envion Health*. 2021;47(8):565–581. doi:10.5271/sjweh.3982

Objectives Chronic low-grade inflammation has been identified as a key pathway linking stress experience to human health. However, systematic evaluations on the relationship of work stress and immune function are scarce and predominantly based on cross-sectional studies. We performed a systematic review and meta-analysis of prospective studies on associations of working conditions and inflammatory biomarkers.

Methods In line with our previously established study protocol and the PRISMA-guidelines, we systematically searched electronic databases for prospective studies on working conditions as well as workplace interventions and inflammatory markers in employees. We classified studies (by design, type of exposure/intervention, outcome) and performed rigorous risk-of-bias assessments. Studies were summarized qualitatively, and a meta-analysis was conducted.

Results We identified 23 eligible studies (N=16 432) with a broad scope of working conditions and inflammatory markers. For interventional designs, we differentiated between individual-directed/behavioral (including physical and mental) and organization-directed/structural interventions. Workplace physical exercise interventions were associated with a decrease in C-reactive protein (k=5; d=-0.61; P<0.001). For other workplace interventions, ie, mental and organizational/structural, results were inconclusive. Concerning observational studies, dimensions of the job demand–control(–support) model were most frequently investigated, and results showed weak – if any – associations with inflammatory markers.

Conclusions The research base was heterogeneous and high-level evidence was limited. More prospective studies are needed with broader consideration of work stressors and inflammatory markers. For practical occupational health management, exercise interventions are effective measures to reduce chronic low-grade inflammation.

Key terms health; immune system; inflammatory biomarker; information and communication technology; job; occupational stress; work.

Given the profound transformation of work in the age of digitalization, investigations into ramifications for employee health are of crucial importance. There is substantial evidence for associations between exposure to workplace-related stressors and risk of physical as well as mental morbidity, including cardiovascular diseases (CVD), metabolic conditions, depression, etc, and mortality (1–9). Over the past years, research on work stress has expanded the focus on job task characteristics [such as described in Karasek's job strain model (10)] to organizational factors (such as working hours or organizational justice) and also broader labor market conditions (such as job insecurity) and their effects on employee health (11–14). Work stress is typically classified as chronic stress, ie, prolonged or repeated stress exposure, although there is no clear time point to dif-

1 Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany.
2 Chair of Health Psychology, Institute of Psychology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany.
3 Institute for Patient Safety, University Hospital Bonn, Bonn, Germany.

Correspondence to: Helena C. Kaltenegger, MSc, Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstraße 1, 80336, München, Germany. [E-mail: helena.kaltenegger@med.uni-muenchen.de]

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ferentiate between chronic and acute stressors (15–17).

In general, the human stress response involves – besides the engagement of the main stress systems [ie, autonomic nervous system (ANS) and hypothalamic-pituitary-adrenocortical (HPA) axis] – complex effects on the immune system most importantly with up-regulation of inflammatory pathways and down-regulation of cellular immunity (18–21). While in the short term these adaptations serve protective functions (22, 23), sustained and systemic low-grade inflammation implies a dysregulation of the immune system and has been suggested as a mediator in the pathogenesis of chronic diseases (20, 24–27). Particularly, inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), but also leukocytes, are involved in the atherosclerotic process (28, 29).

Reviews and meta-analyses in the field of psychoneuroimmunology demonstrate a large body of evidence that psychosocial distress affects immunological and inflammatory activity (17, 30–32). Specifically for work stress, studies reported associations between adverse working conditions and chronic low-grade inflammation in employees, as for instance effort–reward imbalance (ERI) (33), long working hours (34), job strain and poor social support (35, 36). However, two pivotal limitations arise from the current literature base.

First, conclusive and systematic syntheses of the current knowledge base as well as quantitative aggregation of effects of work-related stress on employees' chronic low-grade inflammation are scarce. Previous reviews and meta-analyses have focused on associations of psychosocial job stress (37, 38) and herein particularly ERI (39) with immune and inflammatory markers. Those reviews have the limitation of including a significant number of cross-sectional studies, what limits inferences concerning cause-effect relationships.

Secondly, collated evidence is lacking with regard to effects of other work exposures – besides the commonly studied psychosocial work factors – on employees' immune function. With the ubiquitous and ever-increasing use of information and communication technologies (ICT) in the workplace, associated risks of professionals' stress experience have become a phenomenon of growing scholarly interest. Human interaction with ICT at work is suggested as a potential source of negative psychological and biological sequelae for health and well-being (40, 41). Yet, as far as we are aware, knowledge gaps exist with respect to how working conditions related to the omnipresence and use of ICT and concomitant new demands, but also resources for employees (42) have effects on physiological stress responses in terms of low-grade inflammation.

A review based on prospective studies allows for conclusions on a higher level of evidence and for inferences concerning temporal order and direction of effects in the interplay of workplace stressors and inflammatory reactivity as a risk factor to serious long-term diseases (43). Beyond temporal sequence, ie, the exposure precedes the outcome, one important indicator of causation is reversibility, ie, mitigation of work stress reduces the health risk (13, 44). The consideration of interventional studies with high-quality designs [ie, randomized trials (45)] in addition to observational prospective studies, may therefore not only provide a more complete summary of the evidence, but also deeper insights into potential cause-effect relationships between work stressors and inflammatory markers.

We conducted a systematic review and meta-analysis to determine the present evidence base on prospective associations between various working conditions and chronic low-grade inflammation in employees. More specifically, we aimed to (i) systematically summarize the current research base and establish quantitative estimations of associations. Furthermore, we sought to (ii) detect studies on ICT use at work and inflammatory markers. Lastly, we aimed to (iii) identify and evaluate workplace-related interventions to decrease inflammation.

Methods

Protocol and registration

First, a systematic review protocol was developed and published (46). The review was registered in the PROSPERO-database (registration ID: CRD42020166887). It adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (47; PRISMA-checklist upon request). No major deviances from the original protocol were undertaken. Minor adaptations related to the use of software, waiver of graphical synthesis, and use of AMSTAR-2 instead of GRADE (for details, please see below).

Eligibility criteria

We searched for studies on associations between working conditions and inflammation fulfilling the following PECOS/PICOS-criteria: *Participants (P)*: adult employees/workers/professionals. Clinical samples with particular diagnoses as well as specific professional groups, like military personnel, athletes, artists, and students were excluded. *Exposures/interventions (E/I):* all kinds of working conditions and workplace-related interventions, including psychosocial, mental, and physical. There were no a-priori restrictions by type of workplace intervention, meaning all measures aiming at occupational health promotion or well-being on the job, conducted on or off site as well as during

or outside working hours, were considered. Studies on environmental hazards, ie, chemical or biological agents and extreme heat, as well as nutritional, pharmaceutical, or nutraceutical interventions were not eligible. Furthermore, we excluded studies on shiftwork and exclusive shiftwork samples (48, for a review) as well as studies on socioeconomic status as exposure. A particular objective of our review were effects of work-related use of digital technologies and media, defined as all electronic devices (hardware), applications (software), and means of communication, such as computers, mobile phones, messaging systems, autonomous systems, etc. *Comparators (C):* workers not or exposed to a lower extent to working conditions/workplace interventions of interest. *Outcomes:* pre-defined biomarkers of inflammation within three main categories (cells, plasma molecules, intracellular processes) measured in blood or saliva (see supplementary material, www.sjweh.fi/article/3982, table S1). *Study design (S)*: prospective studies with at least one follow-up measure, ie, at least two consecutive measurements of the inflammation outcome. We included observational (eg, cohort) and interventional studies, ie, randomized controlled trials (RCT) and non-randomized studies of interventions (NRSI, eg, before-after studies). Laboratory or simulation studies were not eligible. We included original research articles in the languages English or German published in peer-reviewed journals from 1982 until present. Conference proceedings, study protocols, and theses were excluded.

Information sources

As primary information source, we conducted a systematic search in five electronic databases, including PubMed/MEDLINE, Embase, PsycINFO, Web of Science, and Cochrane's CENTRAL. Our search was finalized in November 2020. In addition, we performed citation searching of included studies in Google Scholar (forward search) and hand-searching of reference lists of included studies and relevant reviews (backward search).

Search and study selection

We developed a four-tier search string comprising a broad spectrum of terms related to the specified PECOS/PICOS elements (see also 46). The four blocks were linked with the Boolean operator "AND" and within the blocks the terms were combined by "OR". The screening procedure of retrieved records was conducted in Rayyan (49). Two reviewers independently performed systematic and stepwise assessment of eligibility (HK, MW). First, titles and abstracts were screened and then full-texts were assessed. The title and abstract screening were pre-tested, in order to ensure a joint understanding of the eligibility criteria. Discrepancies and uncertainties were resolved by discussion as well as consultation of other review members until consensus was reached.

Data collection process and data items

Two reviewers (HK, MW) extracted data of included studies in a pilot-tested Excel sheet (table S2) that was based on the Cochrane Consumers and Communication Group's template (50). In case of missing information, we contacted authors. We obtained additional data from four authors. For multiple publications of identical data, only one study with longer follow-up period was included. Information was extracted on (46): study characteristics (authors, year, design, location, follow-up, occupational setting); *P*=participants' professional characteristics, age, gender, ethnicity, health-related variables, sample size, recruitment method, relevant inclusion/exclusion criteria; *E/I and C*=type and description of working condition/workplace intervention and comparators, theoretical foundation, and assessment; *O*=type and assessment of outcomes; statistical analyses, results, and moderators/control of confounders. Where reported, we extracted data from adjusted models for baseline biomarker levels and/or important covariates such as age or sex. After data extraction, professional samples were grouped into occupational settings based on the ILO classification of industries and sectors (51).

Risk of bias in individual studies

Two reviewers (HK, MW) performed standardized risk of bias (RoB) assessments, and systematic evaluations were established after consensus. For RCT, the updated version of the commonly used Cochrane risk-of-bias tool (RoB 2; 52), and for NRSI, ROBINS-I was applied (53). Observational studies were assessed with the Quality of Reporting of Observational Longitudinal Research checklist (54). A summary score was calculated with higher scores indicating better quality (54).

Synthesis of results

Synthesis of results comprised three steps: First, we clustered studies by design, exposure/intervention, and outcome. Concerning exposures/interventions, we applied our pre-defined classification system: studies were categorized based on underlying theoretical models and specific exposure features: mental versus non-mental, acute versus chronic, investigation of digital technology use (for definitions, see above and 46). Second, we provided a qualitative summary of all included studies in narrative and tabular format. In addition, main results were visualized by means of arrows indicating direction of effects. Third, where possible, we performed

quantitative syntheses of sufficiently similar studies. Otherwise, results were summarized narratively for at least two studies within one cluster. A random-effects meta-analysis was conducted utilizing Meta-Essentials (55). Heterogeneity was evaluated using Q statistic with p-value and I^2 statistic. In case of low heterogeneity, additionally a fixed-effects model was applied. As the majority of studies were based on controlled designs with repeated measurements, we chose an effect size that accounts for pre-post changes in different groups. In particular, we calculated the recommended pretest-posttest-control group effect size d_{ppc2}, according to the following formula (56, 57):

$$d_{ppc2} = c_P \left[\frac{(M_{post,T} - M_{pre,T}) - (M_{post,C} - M_{pre,C})}{SD_{pre}} \right]$$

$$SD_{pre} = \sqrt{\frac{(n_T - 1)SD_{pre,T}^2 + (n_C - 1)SD_{pre,C}^2}{n_T + n_C - 2}}$$

$$c_p = 1 - \frac{3}{4\,(n_T + n_C - 2) - 1}$$

(*T*=treatment group; *C*=control group)

For the interpretation, the operational definition by Cohen (58) of d-values of 0.2, 0.5, and 0.8 representing small, medium, and large effect sizes was used. As a sensitivity analysis, we excluded studies attributed a high RoB.

Risk of bias across studies

In order to assess RoB across studies, we used funnel plots, tests for funnel plot asymmetry (59), and the Trim-and-Fill procedure (60, 61). Furthermore, we applied the appraisal instrument AMSTAR-2 for evaluation of the quality of our review (62).

Results

Study selection

The database search yielded a total of N=28 623 records. After removal of duplicates, 24 062 records remained and were screened by title and abstract; 23 956 records were discarded. Besides, we identified 2285 additional records and 3 reviews relevant to our research question, which were screened for further eligible studies (38, 63, 64). In total, 106 full-texts were assessed in detail, of which 83 studies did not meet our inclusion criteria (list of excluded studies upon request). Eventually, 23 studies were included in the qualitative and 5 studies in an additional quantitative analysis. A PRISMA flow diagram depicts the study selection process (figure 1).

Study characteristics

The characteristics of all included studies are presented in table 1. There were two major clusters of study designs: 16 interventional studies, including 8 RCT (65–72) and 8 NRSI (73–80) as well as 7 observational studies (81–87). The majority of studies (k=13) (65–68, 70, 73, 75–77, 79, 80, 84, 86) came from Europe, 4 from Asia (71, 72, 83, 87), and 2 from the USA (69, 78) (location in 4 studies not specified). In sum, data from N=16 432 (including dropouts, see table S2) participants were included in our review. Samples were based on different occupational settings, most frequently public service (k=7) (68, 70, 73, 78, 82, 84, 86), followed by health services (k=5) (65, 67, 69, 77, 85). The majority of studies excluded employees with particular diseases, such as CVD, diabetes, inflammatory conditions, and/or use of specific medication (table S2, for more details). We found high heterogeneity in studied work-related exposures/interventions. According to our pre-defined scheme for model- and feature-based classification of working conditions (46), we retrieved 5 studies that were based on established job stress models, including job demands and resources like job control, decision latitude, and workplace social support (73, 82, 83, 86, 87). Other or modified job stress models were examined in 2 studies (84, 85). Concerning specific features, we categorized 15 studies as investigating psychosocial or mental working conditions/interventions (65, 66, 69, 72–74, 76, 78, 80, 82–87) and 8 studies as assessing physical work-related exposures/interventions (67, 68, 70, 71, 75, 77, 79, 81). Furthermore, 3 studies (72, 74, 81) examined predominantly acute effects. Remarkably, we did not retrieve prospective studies on work-related ICT use, apart from one study reporting effects of a web-based workplace intervention (66). Concerning inflammatory outcomes, included studies covered all pre-defined categories (table S1). Most frequently surveyed were plasma molecules including CRP (67, 68, 70, 71, 73, 75, 77–80, 82–84, 86, 87) and cytokines (66, 67, 71, 73, 74, 79–82, 84–86). Inflammation-related processes on cell level, ie, leukocyte counts, were investigated in 3 studies (72, 85, 87). Intracellular processes, including gene expression (65, 72) and transcription factors (69), were also assessed in 3 studies (see tables 1 and S2).

Risk of bias within studies

The results of the RoB assessments (per domain and overall) for RCT and NRSI as well as of the quality of

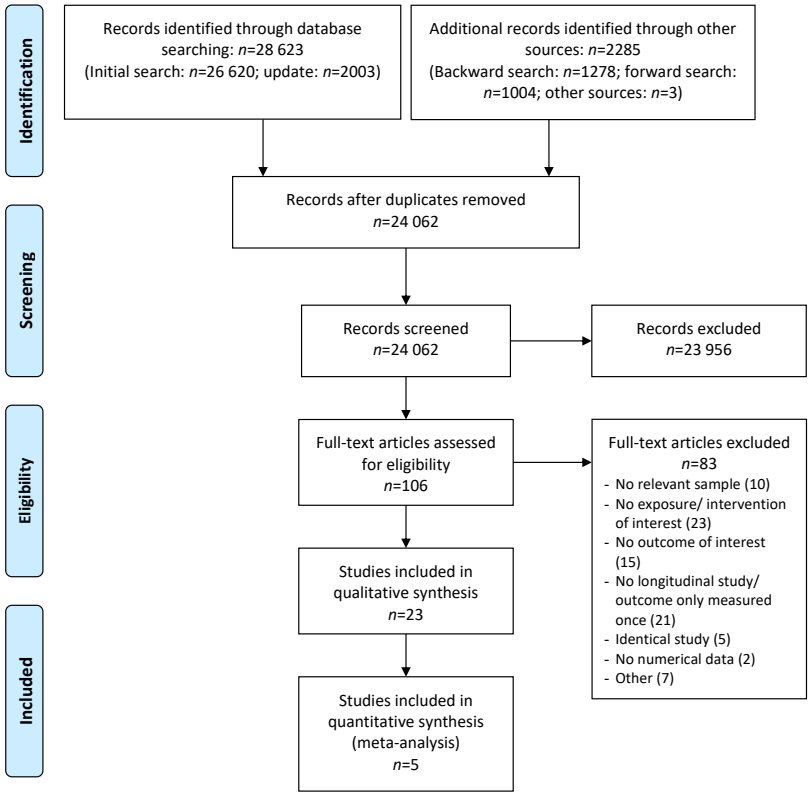

Figure 1. PRISMA flow chart according to Moher et al (47).

reporting assessment for observational studies are shown in table S3. All RCT were appraised to have "some concerns" regarding their overall RoB. Evaluations for NRSI are presented separately for controlled and uncontrolled studies and ranged from "serious" to "critical" overall RoB. For observational studies, on average 20 of the 33 checklist criteria were reported, leading to a mean summary score of 0.62 (range 0.41–0.70).

Results of individual studies

In the following, results are described first for interventional and second for observational studies. For interventional designs, we further distinguished between individual/behavioral (ie, physical and mental) and organizational/structural interventions.

Interventional studies

Individual/Behavioral Interventions

Physical Interventions. We found seven studies assessing effects of workplace physical activity/exercise interventions on inflammatory biomarkers, including five controlled (four RCT) and two uncontrolled studies. With regard to RCT, two studies examined effects of worksite aerobic exercise interventions in laboratory (67) and cleaning personnel (68). Murphy et al (70) investigated the influence of a walking program in civil servants. Respective control groups (CG) received either no training (67, 70) or lectures (68). In a further RCT, effects of a workplace-based yoga intervention were assessed in industry employees against a wait-list CG (71). A controlled study (ie, comparison to passive CG) investigated a cycling to work intervention in professionals of a health insurance company (75). Two uncontrolled NRSI were identified: a leisure time physical activity program in a road maintenance company initiated by the employer (79) and a promotional campaign for stair use in a hospital (77). All studies explored plasma molecules, most frequently CRP. Results per marker are presented in table 2.

A meta-analysis was performed for CRP based on the five controlled studies (see figure 2). Results showed a combined effect size of Cohen's d=-0.61 (range -1.04– -0.18) that was significantly different from zero [z(242)=-3.47, P<0.001, 95% confidence interval (CI) -1.09– -0.12]. This effect was medium-to-large in size and indicated that the physical interventions resulted in a significant reduction of workers' CRP levels. The studies included in this pooled effect size showed no significant heterogeneity (Q=5.64, P =0.228, I^2=29.1%). An additional fixed-effects meta-analysis revealed similar results. Exclusion of one study appraised with "serious" RoB (75) resulted in an attenuated, yet still significant negative effect (d=-0.48, 95% CI -1.04–0.08, P=0.003).

With regard to other inflammatory markers, three

Table 1. Study characteristics (N=23). [CRP=C-reactive protein; hs-CRP=high-sensitivity C-reactive protein; IFN-γ=interferon-gamma; IL=interleukin; JDC(S)=job demand–control(–support) model; MCP-1=monocyte chemoattractant protein-1 (MCP-1); NR=not reported; NRSI=non-randomized study of intervention; RCT=randomized controlled trial; TNF-α=tumor-necrosis-factor-alpha; W=women].

Study	Location	Design	Occupational setting	Sample size	Sex (% W)	Age, mean (SD)	Exposure/ Intervention	Outcome: category	Outcome: biomarker
Carlsson et al (73)	Denmark	NRSI	Public service	359	73.8	49.4 (0.4)	Workplace reorganization	Plasma molecules	CRP, fibrinogen, IL-6
Christian & Nussbaum (81)	NR	Observational	Mixed	24	20	32.4 (7.4); 26.4 (7.7) [a]	Occupational physical demands	Plasma molecules	IL-6
Dich et al (82)	NR	Observational	Public service	7007 [c]	30	49 (5.8)	JDC	Plasma molecules	CRP, IL-6
Dunne et al (65)	Ireland	RCT	Health services	42	NR	NR	Attention-based training program	Intracellular processes	Gene expression (TNF-α, IL-6)
Eguchi et al (83)	Japan	Observational	Mechanical and electrical engineering	2020	26.4	35.9 (10.4); 39.6 (10.1) [b]	Workplace social support	Plasma molecules	hs-CRP
Elovainio et al (84)	England	Observational	Public service	4408	27.3	43.9	Organizational justice	Plasma molecules	hs-CRP, IL-6
Filaire et al (74)	NR	NRSI	Education	9	22.2	42.5 (2.4); 39.2 (2.5) [b]	Lecturing to students	Plasma molecules	IL-10, IL-2, IL-4, TNF-α
Geus et al (75)	Belgium	NRSI	Financial services/ professional services	80	NR	49 (7); 43 (5) [a]	Cycling to work	Plasma molecules	CRP
Hasson et al (66)	Sweden	RCT	Media; culture; graphical	303	38.3	NR	Web-based stress management system	Plasma molecules	TNF-α
Hewitt et al (67)	England	RCT	Health services	20	NR	42 (8); 41 (8) [a]	Aerobic exercise program	Plasma molecules	CRP, TNFα, IL-6
Korshøj et al (68)	Denmark	RCT	Public service	116	75.9	45.3 (8.6)	Aerobic exercise intervention	Plasma molecules	Fibrinogen, hs-CRP
Lebares et al (69)	US	RCT	Health services	83 [d]	48.2 [d]	28.6 (2.7) / 28.7 (2.2); 27.4 (2.1) / 28.8 (2.4) [a]	Enhanced stress resilience training	Intracellular processes	AP-1, NF-kappa B
Lee et al (85)	NR	Observational	Health services	41	100	29.9	Job stress	Cells, plasma molecules	White blood cells, IL-1β, IFN-γ, TNF-α
Magnusson Hanson et al (86)	England	Observational	Public service	4638	28	49.6 (6.0)	JDCS	Plasma molecules	hs-CRP, IL-6
Meyer et al (77)	Switzerland	NRSI	Health services	77	54.5	42.8 (9.0)	Promotional campaign of stair use	Plasma molecules	hs-CRP
Murphy et al (70)	Northern Ireland	RCT	Public service	37	64.9	41.5 (9.3)	Walking intervention	Plasma molecules	hs-CRP
Netterstrøm & Hansen (76)	Denmark	NRSI	Public transport	40	35	44.5; 43.5 [a]	Outsourcing	Plasma molecules	Fibrinogen
Ramey et al (78)	US	NRSI	Public service	38	23.7	41.0 (7.6)	Resilience training	Plasma molecules	CRP
Shete et al (71)	India	RCT	Mixed	48	0	41.5 (5.2)	Yoga training	Plasma molecules	IL-6, TNF-α, hs-CRP
Shirom et al (87)	Israel	Observational	Mixed	1121	34.2	47 (~9)	JDCS	Plasma molecules, cells	hs-CRP, fibrinogen, white blood cell count
Skogstad et al (79)	Norway	NRSI	Construction	121	36	41.8 (12); 42.6 (12.5) [b]	Leisure-time physical activity intervention	Plasma molecules	CRP, IL-6, TNF-α, MCP-1
Wachi et al (72)	Japan	RCT	Mixed	40	0	38.4 (8.4)	Recreational music-making	Intracellular processes; cells	IFN-γ mRNA, IL-2 mRNA, IL-6 mRNA, IL-10 mRNA, Leukocyte counts
Wultsch et al (80)	Austria	NRSI	Mixed	34	11.8	36.4 (8.9); 42.3 (11.2) [a]	extended working periods	Plasma molecules	CRP, IL-6

[a] Age reported separately per group (control, intervention).
[b] Age reported separately for men and women.
[c] Only 39% of the initial sample (with complete biomarker data) were relevant to this review.
[d] Pooled data of two trials.

Table 2. Workplace physical interventions and inflammatory biomarkers. Order of studies per biomarker, by risk of bias assessment, and alphabet. [CG=control group; CRP=C-reactive protein; IG=intervention group; IL-6=interleukin 6; TNF-α=tumor-necrosis-factor-alpha; ↓↓ Significant decrease in inflammatory biomarker following intervention (and no significant change/ increase in control); ↓ Tendency for decrease in inflammatory biomarker, non-significant (and no change/ increase in control); — No significant differences in inflammatory biomarker (between groups/ within group); ↑ Tendency for increase in inflammatory biomarker, non-significant (and no change/ decrease in control); ↑↑ Significant increase in inflammatory biomarker following intervention (and no change/ decrease in control)]

Marker and study	Type of physical intervention (duration, frequency)	Follow-up: period/number	Key findings	Direction of effect
CRP				
Hewitt et al (67) [a]	Aerobic exercise (brisk walking/light jogging, 12 weeks, 4 times/week)	12 weeks/3	IG: significant reductions (week 1-4, 1-8), non-significant reduction (week 1-12) CG: no significant changes Between groups: no significant differences	↓↓ (week 1-4, 1-8) ↓ (week 1–12)
Korshøj et al (68) [a]	Aerobic exercise (indoor biking/running, 12 months, 2 times/week)	12 months/1	IG: no significant changes CG: significant increase Between groups: significant difference	↓
Murphy et al (70) [a]	Walking (8 weeks, 2 days/week)	8 weeks/1	IG: no significant changes CG: no significant changes Between groups: no significant difference	↓
Shete et al (71) [a]	Yoga (3 months, 6 days/week)	3 months/1	IG: significant reduction CG: no significant change Between groups: no significant difference	↓↓
Geus et al (75) [b]	Cycling to work (1 year, at least 3 times/week)	12 months/2	IG: no significant changes CG: no significant changes Between groups: no significant differences	↓
Skogstad et al (79) [c]	Leisure time physical activity (8 weeks)	15 months/2	Significant reduction (at 15 months)	↓↓
Meyer et al (77) [c]	Stair use (12 weeks)	6 months/2	No significant changes following intervention	—
Fibrinogen				
Korshøj et al (68) [a]	Aerobic exercise (indoor biking/running, 12 months, 2 times/week)	12 months/1	IG: no significant change CG: significant increase Between groups: no significant difference	—
IL-6				
Hewitt et al (67) [a]	Aerobic exercise (brisk walking/light jogging, 12 weeks, 4 times/week)	12 weeks/3	IG: No significant changes CG: significant increase (week 1-4) Between groups: no significant differences	—
Shete et al (71) [a]	Yoga (3 months, 6 days/week)	3 months/1	IG: significant reduction CG: no significant change Between groups: significant difference	↓↓
Skogstad et al (79) [c]	Leisure time physical activity (8 weeks)	15 months/2	Significant reduction (at 15 months)	↓↓
TNF-α				
Hewitt et al (67) [a]	Aerobic exercise (brisk walking/light jogging, 12 weeks, 4 times/week)	12 weeks/3	IG: significant reduction (week 1-4), non-significant reductions (week 1-8, 1-12) CG: no significant changes Between groups: no significant differences	↓
Shete et al (71) [a]	Yoga (3 months, 6 days/week)	3 months/1	IG: significant reduction CG: no significant change Between groups: significant difference	↓↓
Skogstad et al (79) [c]	Leisure time physical activity (8 weeks)	15 months/2	No significant changes	—

[a] Randomized controlled trial.
[b] Non-randomized study of intervention, controlled.
[c] Non-randomized study of intervention, uncontrolled.

studies examined pro-inflammatory cytokines and two found reductions in IL-6 (71, 79) and TNF-α (67, 71), respectively.

Mental Interventions. We identified five studies on mental interventions, including four RCT (65, 66, 69, 72) and one uncontrolled study (78). Two RCT scrutinized meditation- and/or mindfulness-based trainings, one among emergency department professionals (65) and one in medical residents (69). Similarly, a resilience training was examined in an uncontrolled study among law-enforcement officers (78). Hasson et al (66) evaluated a web-based health promotion tool in IT and media workers, which in the intervention group (IG) additionally included classical stress management exercises (eg, time-management, relaxation) and a chat. A cross-over study assessed recreational music-making, ie, group drumming, in male corporate employees (72). All results are presented in table S4. Concerning gene expression, findings were mixed with two significant intervention effects, ie, an upregulation

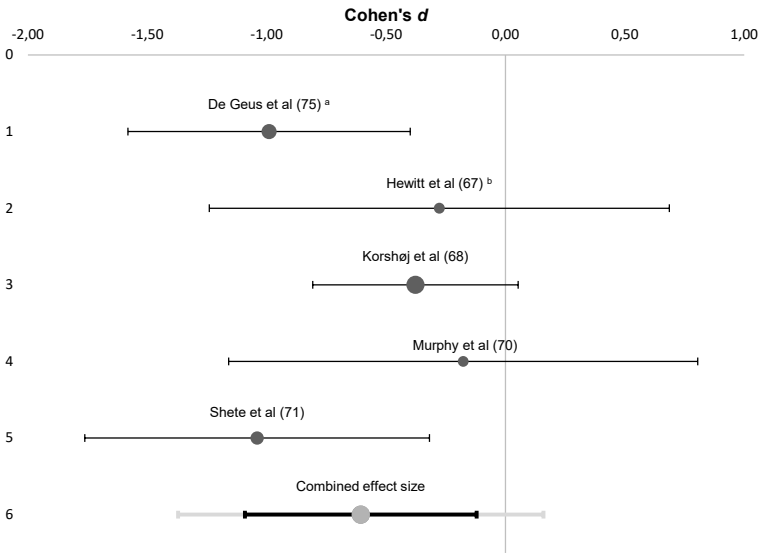

Figure 2. Forrest plot of individual and combined effect size(s) for workplace physical interventions and C-reactive protein. [a] Geus et al (75): results apply to the total study group (including men and women). [b] Hewitt et al (67): only the last follow up measure (after 12 weeks) was considered for this meta analysis.

of TNF-α mRNA (65) and a downregulation of IL-10 mRNA (72), and non-significant effects for other cytokine mRNA levels.

Organizational/Structural Interventions

We found four NRSI on organizational/structural interventions. Two studies assessed effects of work reorganization. One investigated changes in physiological markers following a major reorganization of non-state public offices (73), and another measured physiological effects of outsourcing among bus drivers (76). Wultsch et al (80) examined inflammatory effects of extended daily working times in office workers and carpenters. In addition, we included one study among university professors that investigated acute inflammatory reactions in saliva after lecturing to students (74). All results are depicted in table S5. Due to "serious" and "critical" RoB appraisals, reported findings need to be interpreted with caution. The two studies that measured employees' CRP found significant increases after the intervention (73), yet one just in younger participants (80). For fibrinogen, no studies showed significant changes (73, 76). Regarding cytokines, for IL-6 one (73) out of two studies (80) reported significant upregulations. For other cytokines, increases were observed in response to an acute work stressor, ie, lecturing (except for IL-10) (74).

Observational studies

Overall, seven observational studies were retrieved (table 3). Four studies (82, 83, 86, 87) applied Karasek's job demand–control(–support) JDC(-S) model (10, 88): Job strain (82, 86, 87) and workplace social support (86, 87) were not prospectively related to CRP. Meanwhile, when the source of social support was specified, high supervisor support (in contrast to coworker support) was associated with lower CRP among women but not men (83). Job demands were not related to fibrinogen and leukocyte count (87) as well as IL-6 (82, 86). However, there were indications for small protective effects of job control regarding fibrinogen (87) and IL-6 (86) among women and leukocyte counts among men (87). For social support, Shirom et al (87) found no effects, but notably Magnusson Hanson et al (86) showed that poor workplace support – albeit weakly – was linked to higher IL-6 levels, which partially mediated the association with diabetes. Lee et al (85) investigated job stress in hospital nurses based on criteria related to the JDC(-S) model by comparing measures of objective (eg, data on staffing patterns) and subjective (ie, self-report data) stress: they identified significantly lower numbers of white blood cells in the group with high objective stress, but found no effects of subjective stress and for cytokines (85). Moreover, organizational justice and inflammation were surveyed in a large cohort study (84): Among men, but not women, low self-reported justice was associated with increased CRP and IL-6 in the long-term. Besides these model-based studies, we found one small exploratory study that compared acute effects of occupational physical demands in two groups with high (eg, construction workers) and low (ie, sedentary work) risk of work-related musculoskeletal disorders (81): IL-6 levels were greater in the high-risk group yet showed opposed temporal patterns in the two groups (table 3).

Risk of bias across studies

Concerning the meta-analysis, the funnel plot indicated symmetry in the distribution of individual effect estimates suggesting absence of bias and heterogeneity (89). As less than ten studies were included, tests for asymmetry were not used (90). Based on the Trim-and-Fill

Table 3. Work-Related Exposures and Inflammatory Biomarkers [CRP=C-reactive protein; IFN-γ=interferon-gamma; IL=interleukin; JDC(S)=job demand-control(-support) model; NS=not significantly/ no significant; TNF-α=tumor-necrosis-factor-alpha. ↑↑ Significant positive association between working condition and inflammatory biomarker; ↑ Tendency for positive association between working condition and inflammatory biomarker, non-significant; — No significant association between working condition and inflammatory biomarker; ↓ Tendency for negative association between working condition and inflammatory biomarker, non-significant; ↓↓ Significant negative association between working condition and inflammatory biomarker; ↑↑* Significant increase in inflammatory biomarker (group comparison); ↑* Tendency for increase in inflammatory biomarker, non-significant (group comparison); —* No significant differences in inflammatory biomarkers (group comparison); ↓* Tendency for decrease in inflammatory biomarker, non-significant (group comparison); ↓↓* Significant decrease in inflammatory biomarker (group comparison).]

Marker and study	Type of exposure	Follow-up: period/ number	Key findings	Direction of effect
CRP				
Dich et al (82)	JDC	~10-11 years/2	Job demands, decision latitude, job strain NS correlated with CRP	—
Magnusson Hanson et al (86)	JDCS	10 years/2	Job demands, job control, job strain, workplace social support NS associated with subsequent CRP	—
Shirom et al (87)	JDCS	18-22 months/1	Workload, perceived control, social support NS associated with CRP	—
Eguchi et al (83)	Source-specific workplace social support (supervisor, coworker)	1 year/1	Supervisor support significantly negatively related to CRP in women (β=-0.11, P<0.01), not significantly related to CRP in men Coworker support NS related to CRP	↓↓ (supervisor support, women)
Elovainio et al (84)	Organizational justice	~ 14 years/2	Organizational justice significantly negatively associated with CRP in men (percentage change: -4.0, P=0.02); no associations in women	↓↓ (men) — (women)
Fibrinogen				
Shirom et al (87)	JDCS	18-22 months/1	Workload NS associated with fibrinogen Control significantly negatively associated in females (β=-0.09, P<0.05), no associations in males Social support NS associated with fibrinogen	Workload — Control ↓↓ (women) Support —
IFN-γ, IL-1β and TNF-α				
Lee et al (85)	Job stress (objective and subjective job stressors: low vs. high)	8 months/8	IFN-γ: NS differences between low vs. high objective and subjective job stress IL-1β: NS differences between low vs. high objective and subjective job stress TNF-α: Marginally lower level of TNF-α (ng/ml) in high objective job stress group (Mdn=1.7) compared to low (Mdn=2.2, P=0.07) NS differences between low vs. high subjective job stress	—* —* ↓*
IL-6				
Dich et al (82)	JDC	~10-11 years/2	Job strain, job demands, decision latitude NS correlated with IL-6	—
Magnusson Hanson et al (86)	JDCS	10 years/2	Social support [a] associated with subsequent IL-6 (β=0.03, P=0.051) Job demands and control [a] NS associated with subsequent IL-6 Sex stratified analyses: Job control [a] significantly associated to subsequent IL-6 in women (β=0.07, P<0.05), not men	Support [a] ↑ Demands — Control — Control [a] ↑↑ (women)
Christian & Nussbaum (81)	Occupational physical demands (high vs low)	1 working week/5	Higher IL-6 levels in high risk group (at all time points) Interaction time x group (F=2.53, P=0.07)	↑* ↑↓* (high) ↓↑* (low)
Elovainio et al (84)	Organizational justice	~ 14 years/2	Organizational justice significantly negatively associated with IL-6 in men (percentage change: -4.5, P=0.01); no associations in women	↓↓ (men) — (women)
Leukocyte count				
Lee et al (85)	Job stress (objective and subjective job stressors: low vs. high)	8 months/8	Significant lower level of white blood cells (number of cells per mm^3) in high objective job stress group (Mdn=7.17) compared to low (Mdn=8.06, P=0.03) NS difference between low vs. high subjective job stress	↓↓*
Shirom et al (87)	JDCS	18-22 months/1	Workload NS associated with leukocyte count Control significantly negatively associated in males (β=-0.06, P<0.05), NS associated in females Social support NS associated with leukocyte count	Demands — Control ↓↓ (men) Support —

[a] Higher values in the scales for workplace social support and job control indicated lower social support and lower control, respectively (86).

method, no studies were missing to the right of the mean, so the combined effect size did not have to be adjusted for publication bias (see figure S1). Our self-rating of the overall confidence in the results per AMSTAR-2 (62) was "high", indicating that the review provides an accurate and comprehensive summary of available studies addressing our research question (AMSTAR-2 evaluation sheet available upon request).

Discussion

Sustained systemic low-grade inflammation has been identified as one of the major pathophysiological pathways linking exposure to chronic stress and development of severe long-term diseases. A thorough and evidence-based understanding of the role of work stress exposure for inflammatory pathways is thus imperative to develop effective prevention and mitigation measures in occupational stress research. To the best of our knowledge, this is the first systematic review and meta-analysis on

associations of working conditions and chronic low-grade inflammation merely based on prospective studies. By building on a higher quality of evidence, this review advances our knowledge on effects of work stressors on chronic low-grade inflammation in employees.

Overall, 23 studies met our inclusion criteria. The extant study base was fragmented with high heterogeneity in assessed exposures and interventions. We identified four clusters of study types, ie, individual-directed/behavioral (including physical and mental) and organization-directed/structural interventions as well as observational studies.

For workplace *physical interventions* (k=7), the majority of studies reported reductions in inflammation-related plasma molecules. These interventions primarily aimed at changing individual behavior by adding physical exercises or activity into employees' work routine (both on- and off-the-job) and were conducted among both sedentary and manual workers. The qualitative finding was corroborated in our meta-analysis demonstrating a medium to strong negative effect of physical exercise interventions (aerobic exercise, walking, yoga, cycling to work) on employees' CRP levels (d= -0.61; k=5). This resonates well with a previous meta-analysis on studies in non-occupational settings showing that exercise training was associated with a decrease in CRP (91). Our results suggest that exercise interventions are an effective measure to reduce low-grade inflammation in employees.

Concerning *mental interventions* in the workplace (eg, stress reduction programs, music making), the study base (k=5) was limited and inconclusive. However, there were indications for changes of inflammation-related processes on intra-cellular level, ie, gene expression (65, 72) and transcription factors (69). These interventions were also individual-oriented, ie, they aimed at influencing mental processes by providing employees opportunities and skills for increasing their well-being, alleviating stress, facilitating relaxation, strengthening resilience etc. Reviews outside work settings have shown associations of psychosocial interventions, especially cognitive behavior therapy and combined psychotherapeutic interventions, with enhanced immune system function (92). In addition, salutogenic effects of mindfulness meditation and yoga practices in combination with mindfulness-based stress reduction regarding specific inflammatory markers have been suggested (93, 94). Yet, these studies included heterogeneous populations, also clinical samples, which can lead to spurious estimates of effects. Our synthesis suggests that in occupational settings, individual/behavioral interventions appear to be viable measures to ameliorate dysregulated inflammatory processes, however extended research into workplace mental interventions is warranted.

The study base on *organizational/structural interventions* was confined, with high RoB (k=4). Despite indications of responsiveness of CRP and cytokines to organizational changes (73, 80), definite conclusions would be premature. Given the high variety of organizational-level workplace interventions and differentiated effects on employee health, further investigations into particular types of organizational interventions, such as work reorganization or work time-related conditions, and their effects on inflammatory markers are necessary (95).

The majority of *observational studies* (k=7) was based on the JDC(-S) model. Results showed predominately null and/or weak associations. However, there were some indications for beneficial functions of job control and workplace social support as well as for sex-related effects. Conclusions of previous reviews are somewhat conflicting: Whereas Nakata (37) suggested that inflammatory markers might be less sensitive to job strain, Wright et al (38) inferred that workplace stress is positively associated with CRP, especially when measured with the JDC model. Despite the evidence for a close link between personal relationships, including social support amongst others, and immune function (96), we found only three studies on workplace social support and inflammatory outcomes. Consistent with previous reviews we deem future research into resources and potentially beneficial effects of workplace support of particular interest (37).

We also sought to detect studies examining stress reactions in terms of inflammation evoked by work-related ICT use. Ultimately, we identified just one study showing that the application of a web-based health promotion tool modulated TNF-α (66). The extent to which working conditions associated with ICT use or respective workplace interventions affect inflammatory processes needs thus to be further investigated.

Work stress and inflammation: methodological and conceptual considerations

For the interpretation of the collected evidence, some pivotal aspects potentially influencing associations of working conditions and inflammation warrant attention. First, included studies differed tremendously in time lags of follow-ups, spanning a few hours to 14 years, and in numbers, ranging from one to eight follow-up assessments. In longitudinal research the magnitude of effects might vary with the span of the follow-up, ie, whether it corresponds with the true underlying time lag of the outcome under study (43). Multi-wave designs increase the likelihood of detecting effects compared to two-wave designs, and response latencies of respective outcomes may depend on type, intensity, and duration of exposures as well as context factors (43, 97). Thus, differences in follow-up measurements of inflammatory markers may help to explain the disparity in findings of the present studies.

Moreover, although longitudinal designs are suggested to overcome the problems of cross-sectional designs in examining causality, reversed or reciprocal causation and third variables constitute critical issues in longitudinal research (98). As for the question of reverse effects, we are aware of only two of the included observational studies that also tested for associations in the opposite direction in full panel designs, ie, inflammatory markers on subsequent appraisal of working conditions (86, 87). Concerning influences of third variables, many studies controlled for variables critical in stress physiology, such as sex, age, health behaviors (eg, physical activity, smoking), body mass index, (hormone) medication, and baseline levels of respective markers. However, studies differed in the selection and number of included covariates, entailing varying degrees of threats to internal validity (see also tables S2 and S3). For the investigation of cause–effect relationships between intervention and outcome, RCT are considered the gold standard; yet this design is often not feasible in occupational settings (99). Notwithstanding, half of the identified interventions were RCT, so we were able to draw our meta-analysis upon a high level of evidence, yet confined study base.

Furthermore, inflammation should not be assessed in isolation with regard to stress but in the light of potential disruptions of interactions and feedback loops with other stress axes. Inflammation is affected by the two major stress systems HPA axis and ANS through complex neuroendocrine-immune cascades and interactions, indicating that the effects of stress system mediators on the inflammatory system are not linear (100). There is consistent evidence that chronic stress is related to alterations in the sensitivity of target tissue to stress signals, most importantly glucocorticoid resistance, which is associated with increases in circulating inflammatory mechanisms (100). Examples of these complex multisystem interdependences are the – at first glance surprising – results of Dunne et al (65), where TNF-α mRNA increased in the IG, and Hasson et al (66), where TNF-α decreased in the CG. Both authors provided post-hoc explanations concerning potentially impaired negative feedback loops with the HPA axis in chronic stress, and Dunne et al proposed that the observed increase could be due to decreases in cortisol following stress reduction in the IG. Anti-inflammatory effects of cortisol have been well-described (100).

Lastly, we focused on working conditions, as they are more modifiable to workplace interventions than personal factors. Nonetheless, we acknowledge that employees' intrinsic characteristics, such as personal resources, affective-cognitive states, and coping styles, play a significant role in (work) stress perception and regulation (101–103). For instance, higher work engagement was found to be associated with lower subsequent high-sensitivity CRP (104), whereas over-commitment was associated with reduced immunity (39).

Limitations and strengths

Our findings should be interpreted in the light of some limitations. By defining the PECOS/PICOS components, we might have excluded relevant aspects. For example, shiftwork is an important risk factor for inflammation, and in our search, we found sound interventional studies in shift worker samples (eg, 105). However, as it is difficult to disentangle effects of working conditions from the effects of circadian misalignment per se on inflammatory markers (106), we decided a priori to exclude these studies. Moreover, for greater external validity, we only considered investigations in real-world occupational settings. Notwithstanding, we are aware of high-quality laboratory studies on stress responsiveness in chronic work stress (107, 108) and simulation studies in high-risk professions, such as firefighting (109). The generalizability of our findings is restricted to the working population, yet we included a broad range of different professional and occupational groups. A main limitation of our review is the limited study base with great heterogeneity regarding intervention contents and modes of implementation, work exposures, and occupational sectors. By clustering studies following an inductive logic we attempted to build more homogenous subgroups of studies. However, the disparity of clusters in combination with the scarcity of data currently limits the possibility and adequacy of deriving overall conclusions. We acknowledge, that some employer-instigated health promotion approaches were not limited to the workplace and included components to be performed off site/ off duty or on the way to work (eg, cycling to work). This may have introduced heterogeneity within our clusters and impeded a clear differentiation concerning the nature and implementation of included interventions as well as ensuing inferences concerning effectiveness. An important strength of our investigation is that we developed and determined our methodology prior to the start in a peer-reviewed protocol, limiting the risk of reporting bias and ensuring higher quality. Further strengths pertain to our pre-defined classification system, which enabled us to draw conclusions per cluster given the high heterogeneity of identified studies, and the consideration of a comprehensive set of inflammatory biomarkers. Furthermore, we applied rigorous and thorough RoB assessments in and across studies, allowing for a critical evaluation of the presented evidence.

Implications for occupational health management and future research

For occupational health management, a holistic approach integrating both individual/behavioral and organizational/

structural measures may generate greater benefits for employee health (110). The reported physical interventions primarily aimed at modifying employees' behaviors, ie, increasing their physical activity to counteract predominantly sedentary work or high aerobic workload (eg, cleaning). Yet, rather than merely reducing symptoms of work-related strain, preventive measures on an organizational level that target the sources of strain are crucial (111). Primary preventive interventions address stressors through changes in the psychosocial working conditions, physical work environment, or organization and include for instance enhancement of social support or autonomy, and job redesign (110, 112, 113). Although we did not find intervention studies directly aiming at modifying psychosocial work stressors, pooled results of the observational studies suggesting protective effects of job control and social support to employees' inflammation indicate that these factors could be important leverage points to future intervention studies. Furthermore, all retrieved interventions referred to unidimensional approaches, what points to the need for evaluation of complementary, multi-component interventions consisting of individual and organizational measures regarding effects on physiological stress parameters (eg, 114.).

In the light of our findings and further considerations, we suggest the following avenues for future research: First and foremost, more prospective studies are needed. For workplace interventions, RCT or at least controlled studies on mental, physical, and organizational interventions are necessary. In observational research, deployment of full cross-lagged panel designs provides reliable insights into the direction of effects. Second, future research should investigate combinations of work exposures, eg, both psychosocial work factors and occupational physical activity. Investigations into potential additive and interactive effects on psychophysical health might better reflect real-world occupational situations. Moreover, we advocate a clear conceptual and methodological differentiation between objective work exposures on the one hand and subjective reactions of the individual workers on the other. For research on psychosocial work stress however, this is often not feasible, as per definition, psychosocial factors at work concern *interactions* between both work environment, job content, organizational conditions and individual factors of the workers, such as capacities, needs etc., which may influence health and well-being (115). Third, future research should examine effects of work-related ICT use on inflammation in occupational settings with high-quality designs. With the dynamic advancement of digitalization and technologization of humans' workplaces, research into the concept of technostress (116–118) has been rapidly increasing. However, physiological effects associated with technostress are under-researched (40), and assessment of inflammatory markers might reveal valuable insights into potential detrimental health effects. Forth, while CRP and cytokines were surveyed most frequently, future research should consider further biomarkers of inflammatory processes (such as cellular and intracellular) and interactions with other stress systems. This will contribute to a deeper understanding of pathophysiological pathways from work stress exposure to disease.

Concluding remarks

This systematic review and meta-analysis on associations of working conditions and chronic low-grade inflammation showed that the current base of prospective studies is limited and diverse in methodology, exposures, and inflammatory outcomes. Meta-analytic evidence was established for workplace physical exercise interventions, which were found to significantly reduce employees' CRP level. Complementary to previous reviews mainly based on cross-sectional studies, our review revealed a more differentiated picture of potential associations, suggesting that at this stage, definite conclusions are premature. The review identified important research gaps and derived recommendations for future high-quality studies to advance knowledge in this field. Concerning occupational health management practice, we conclude that physical activity interventions for employees are effective counter-measures to chronic low-grade inflammation.

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2.3 Paper III

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RESEARCH ARTICLE

Psychosocial working conditions and chronic low-grade inflammation in geriatric care professionals: A cross-sectional study

Helena C. Kaltenegger[1]*, Matthias Weigl[1,2], Linda Becker[3], Nicolas Rohleder[3], Dennis Nowak[1], Caroline Quartucci[1,4]

1 Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany, **2** Institute for Patient Safety, University Hospital Bonn, Bonn, Germany, **3** Chair of Health Psychology, Institute of Psychology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany, **4** Bavarian Health and Food Safety Authority, Institute for Occupational Health and Product Safety, Environmental Health, Munich, Germany

* helena.kaltenegger@med.lmu.de

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Abstract

Background

Chronic low-grade inflammation has been suggested as a key factor in the association between stress exposure and long-term health. Care work is recognized as a profession with a high degree of job stress and health risks. However, for care professionals, the study base on inflammatory activity due to adverse working conditions is limited.

Objective

The aim of this study was to explore associations between self-reported psychosocial working conditions and care professionals' biomarkers of systemic low-grade inflammation.

Methods

N = 140 geriatric care professionals (79.3% females, mean age = 44.1 years) of six care facilities were enrolled in a cross-sectional study consisting of standardized medical examinations and employee surveys. Standardized questionnaires were used for evaluation of psychosocial work characteristics (work overload, job autonomy, social support) based on Karasek's job strain model. Blood samples were drawn for two biomarkers of inflammatory activity: C-reactive protein (CRP) and leukocyte count. Analyses comprised uni- and multivariate logistic and linear regression analyses.

Results

We determined a proportion of 5.4% of care professionals with increased low-grade inflammation. We further observed a relationship between job autonomy and CRP, such that reports of high job autonomy were associated with increased levels of CRP (adjusted OR = 4.10, 95% CI [1.10, 15.26], $p = .035$), which was robust in additional analyses on further

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potential confounders. No significant associations with participants' leukocyte numbers were found.

Conclusions

This exploratory study contributes to the research base on links between workplace stress and ensuing illness in care professionals. Our findings may help to identify risk and protective factors of the work environment for chronic low-grade inflammation. The results require further scrutiny, and future prospective studies on associations of psychosocial working conditions, low-grade inflammation and long-term health outcomes in care professionals are needed.

Introduction

Care work is associated with a substantial level of job stress involving major risks to psychophysiological health [1–3]. Chronic exposure to work stressors has been linked to physical and mental morbidity, including cardiovascular diseases (CVD), type 2 diabetes, clinical depression, etc., as well as mortality [4–8].

An increasing research base indicates that systemic low-grade inflammation as a sub-component of the immune system plays a critical role in the development of chronic conditions [9–12]. Systemic inflammatory markers, such as C-reactive protein (CRP) or circulating leukocytes, are suggested to be involved in the atherosclerotic process [13, 14]. Specifically for exposure to workplace stress, previous investigations revealed relationships between adverse and unfavorable working conditions and chronic systemic low-grade inflammation among employees [15–19]. Persistent workplace stress has been found to impact immune function with higher likelihoods of increased inflammatory activity and reduced adaptive immune function in employees reporting poor psychosocial working conditions [20–22]. This resonates well with existing knowledge and evidence stemming from psychoneuroimmunology that experiences of acute and chronic psychosocial stress affect human immune function and inflammatory processes [9, 23, 24].

Despite its growing importance, the respective research base on work stress, immune function, and inflammatory processes specifically for care professionals is limited and inconsistent [25–27]. Previous investigations into work-related influences on nursing professionals' immune system predominantly surveyed the role of shift work [28, 29], overall professional stress [30, 31], and mediating experiences of job satisfaction [32]. Given the eminent role of psychosocial risk factors and their contribution to long-term health outcomes, protuberant knowledge gaps remain.

First, available studies on the associations of nurses' job stress with immunological and inflammatory biomarkers suggest that high work stress environments affect both cellular and humoral immunity [30, 31, 33–35]. Most studies however, used aggregate measures of job stress and focused on specific branches of the immune system (such as cellular immunity or immunoglobulins). To our knowledge, studies considering different components of psychosocial work stress are scarce [33, 34]. Investigations that take into account different job characteristics, including stressors as well as resources, and their individual as well as interactive effects provide a better understanding of how work stress affects care professionals' immune system.

Second, concerning the role of protective factors at work, a range of psychosocial resources have been scrutinized with particular emphasis on autonomy and social support [2, 36, 37].

However, the current research base remains inconclusive with some hints (yet, outside of nursing) suggesting that high social support and job control are associated with lower inflammation status [18, 19, 38–41].

Third, work stress models have proven useful in understanding the pathways from workplace stress to altered immune and inflammation processes [12]. Among these, one of the most prominent approaches is the job demand-control model (JDC; [42, 43]) and expanded job strain model with its three major components of job demands, control, and social support (JDC-S; [44]). It proposes that work environments with high job demands, low job control and autonomy as well as low levels of social support bear the highest risk for adverse health outcomes [43, 44]. With regard to inflammatory processes, studies that draw upon the job strain model are sparse and report inconsistent results [39, 45, 46]. In care professionals, respective investigations based on work stress models are lacking [12, 32].

To this end, we sought to examine associations between psychosocial working conditions based on the JDC-S model and chronic low-grade inflammation among care professionals. As biomarkers of inflammation, CRP as an indicator of humoral immunity and leukocyte count as an indicator of cellular immunity were analyzed [47]: CRP has long been recognized as one of the most sensitive of the acute-phase reactants. It is a key indicator for inflammation in work stress research with potential CRP-upregulation in response to adverse working conditions [12, 19]. Leukocytes are a promising indicator of immune and inflammatory activity for workplace stress research, as leukocyte subpopulation numbers were shown to be altered in individuals under chronic psychosocial stress [12, 48, 49].

Healthcare professionals may represent an at-risk group for disease vulnerability and progression [27]. In particular, geriatric nurses are exposed to various general work stressors such as time pressure, physical demands and interpersonal conflicts, but also specific stressors pertaining to the emotional burden of caring for patients [50, 51]. Exposure to these stressors is linked to burnout, which in turn is not only associated with adverse consequences for general health on an individual level, but also on an organizational level most importantly regarding quality of care and patient safety [27, 52]. Lastly, high rates of absenteeism and intention to leave among nurses are a concern of global scale [53]. It is therefore crucial to understand how working conditions lead to chronic stress with pathophysiological alterations (i.e., low-grade inflammation) and eventually contribute to pathogenesis. A better understanding of those associations may be used for job design and occupational health management. For instance, a recent participatory workplace intervention study was effective in reducing stress-related inflammation among nurses [54, 55].

Study objectives

Based upon a cross-sectional study, we aimed at exploring individual and synergistic associations of work and individual characteristics with care professionals' inflammatory outcomes. Specifically, we aimed to determine: (1) the prevalence of increased low-grade inflammation among geriatric care professionals; (2) individual and synergistic associations of risk and protective factors of the work environment with low-grade inflammation outcomes in geriatric care professionals.

Methods

Design and ethics

We established a cross-sectional study that combined different data sources of standardized self-reports, medical examinations, and measurement of biomarkers. Our analysis was part of an investigation into care professionals' age and work environment factors [56]. Prior to the

start of the study, ethical approval through the Ethics Committee of the Medical Faculty of Ludwig-Maximilians-University of Munich (No. 99–15) was obtained and agreement was gathered from the study facilities' management and organization. Before data collection, professionals were informed and provided written consent.

Sample

Applying a convenience sampling approach, a total of $N = 140$ employees from six geriatric care facilities in South Germany was included in the study. The sample consisted of geriatric care professionals, mainly nurses but also assisting, kitchen, and cleaning staff. Data were collected in 2015 over the course of three months with weekly visits on site. The sample included 111 females (79.3%). 18 (12.9%) care professionals were working part-time and 116 in a shift work schedule (82.9%). Mean age was 44.10 years (standard deviation, $SD = 12.39$, range 18–69 years) with an average professional tenure of 22.32 years ($SD = 11.98$, range 0.5–50 years). Mean weekly working hours were $M = 37.21$ ($SD = 7.74$, range 7–45 hours). Average BMI was 25.63 ($SD = 4.31$, range 18.3–44.0).

Data collection

The data collection procedure consisted of three consecutive steps: First, a standardized medical history was obtained and an examination was conducted in course of the regular, tri-annual preventive medical check for health care professionals. This assessment is mandatory and performed according to the standards of the German Ordinance on Occupational Health Care [57]. Second, a standardized questionnaire was handed out to each participant. The survey included questions concerning individual characteristics and psychosocial working conditions (all described below). Completed questionnaires were directly returned to the study team in sealed envelopes. Third, a trained occupational physician (study author QC, who also conducted the medical examinations above) withdrew biomarker samples from each professional. Venous blood was collected using serum monovettes (Sarstedt 'S-Monovette®'). Blood samples were immediately stored at 4˚ Celsius and transferred to the laboratory for further processing. All samples were handled according to standard laboratory procedure. During data collection and further processing, pseudonymization procedures were established through study codes on questionnaires, protocols, and laboratory samples. This allowed matching of survey, examination, and biomarker data. Data were anonymized immediately after data collection.

Measures and data sources

Physician examination. The occupational physician evaluated participants' current health status and medical history, including acute and chronic diseases with potential relevance to inflammatory reactions (i.e., current infections, tumors, neuroendocrine disorders, rheumatism, arthritis, CVD, recently obtained surgery, or accidents). Information on current medication intake was collected with particular focus on medication affecting inflammatory processes, such as antibiotics, non-steroidal anti-inflammatory drugs, biologicals and cortisone. Further questions included previous GP-provided diagnoses relevant to our study objectives.

Professionals' psychosocial working conditions. Consistent with the job strain model, our questionnaire included three standardized scales for self-evaluation of the nursing work environment that were drawn from a well-established tool for work analysis in healthcare [58]. This tool was developed for healthcare workplaces and has been repeatedly scrutinized for reliability, factorial and content validity [59–61]. We deployed the following scales [59]:

Work overload was measured with a three-item scale assessing professionals' appraisal of quantitative overload and time pressure at work (item example: 'I often have too much work to do at once'). Answers were obtained on a five-point scale ranging from 1 = 'no, not at all' to 5 = 'yes, to a great extent'. Internal reliability was determined with Cronbach's α = .88.

Job autonomy was assessed with four items (item example: 'My work allows for decisions on which methods I pursue'). This scale measures skill discretion and degrees of freedom at the workplace (scale range: 1 = 'no, not at all' to 5 = 'yes, to a great extent'). Cronbach's α was .87.

Social support was measured with two questions encompassing key sources of social support at work, i.e., direct supervisor and colleagues; item example: 'To what extent do you receive social support from your colleagues such that your work is facilitated?' (scale range: 1 = 'not at all' to 4 = 'to a great extent'). Cronbach's α was .59.

Employment and individual characteristics. The following information on care professionals' employment and individual (sociodemographic and health) characteristics were gathered to control for potential confounders:

Employment information comprised contract (full-time vs. part-time), weekly working hours, and shiftwork (yes vs. no). In addition, employees rated a set of questions concerning adverse work environment conditions (three questions on high noise, poor light, poor climate) as well as physical workload (five items pertaining to demands, e.g., lifting heavy loads, working in unfavorable postures).

Sociodemographic characteristics included sex (female, male), age (in years), and professional tenure (in years).

Health-related information examined by the physician concerned chronic health conditions and health behaviors including diabetes (no risk vs. risk), risk of CVD (no risk vs. risk), smoking (in pack years), and physical activity in leisure time (yes vs. no). Furthermore, body mass index (BMI) was calculated.

Blood samples for biomarkers of inflammation (C-reactive protein, leukocyte count). *C-reactive protein (CRP)*. Serum concentration of CRP was analyzed by immunoturbidimetric method using the AU600/640/640e/680 and AU2700/5400 Beckman Coulter Analyzers. Laboratory reports listed two categories: values < 5 mg/L were reported non-numeric, values > 5mg/L were reported numerical. Therefore, we used this bivariate outcome classification in our data analyses.

Leukocyte count. Leukocytes were analyzed by particle counting (optical-electronic). We considered values between 3.9–10.4 x 10^9 (women) and 3.9–9.8 x 10^9 (men), respectively, as normal range based on the reference values provided by our laboratory and following established reference ranges in the respective literature [e.g., 62].

Statistical analyses

After aggregation of all data sources, prevalence for the outcome variables in the overall sample was determined. Based on the physician's review of examination and laboratory data, we then identified our study group of interest, i.e., professionals with increased low-grade inflammation (characterized by CRP > 5 mg/L and no further medical conditions or known clinical reason for elevated inflammation).

With regard to the study's objectives, regression analyses to obtain risk estimates through bivariate (i.e. crude regression estimates) and multivariate analyses (i.e. regression estimates adjusted for all predictor and control variables) were applied. In the main analyses, we included the control variables sex, age, BMI, shiftwork, weekly working time, and in further analyses, additionally CVD risk, diabetes risk, smoking, professional tenure, physical activity

in leisure time, adverse environmental conditions, and physical demands. For CRP, we applied binary logistic regressions; for leukocyte counts, we used linear regressions.

Consistent with the propositions of the job strain model, we intended to test two main hypotheses: first, the iso-strain hypothesis suggesting additive, main effects of each component [63]. Second, in line with the buffer hypothesis predicting that protective factors such as autonomy or social support can buffer the potential negative effects of job demands on health and well-being, we tested for statistical interactions between the job demand and resources, respectively [63]. To this end, we explored potential moderation effects by including the interactions of work overload x social support and work overload x autonomy as additional predictors in the multivariate analyses (i.e., identification of multiplicative effects).

Prior to all analyses, continuous predictor variables were standardized (through mean-centering) to limit multi-collinearity. Potential multi-collinearity within the multivariate models was examined using correlation matrices and variance inflation factor [64], and results did not indicate critical collinearity among the predictor variables. As an additional analysis, we also applied the logarithmic transformation to the leukocyte count outcome measure. In order to adjust for multiple testing, we controlled the false discovery rate according to the Benjamini-Hochberg method ($\frac{i}{m} \times Q$, where i = rank of p-value, m = total number of tests and Q = false discovery rate) [65]. All analyses were computed with SPSS 26.0 (IBM Inc., Chicago).

Results

Overall sample and selection of study group

Altogether, the sample included $N = 140$ care professionals (see S1 Fig in Supporting Information for a flow chart). First, all professionals with an elevated inflammation level due to acute or chronic medical conditions were identified to avoid spurious estimates of associations between predictor and key outcome measures, i.e., chronic low-grade inflammation. After physician's review, 10 professionals with verified elevated inflammation were excluded (7.1% of the overall group). Medical conditions of excluded professionals were for instance intake of cortisone medication, acute infection, injury from fall, or rheumatism. With regard to sociodemographic and health characteristics, excluded professionals were not significantly different in terms of sex, age, shift work, contract, professional tenure, average working hours, and average BMI compared to the remaining study sample (see S1 Table).

Descriptive statistics of working conditions and low-grade inflammation

In the study sample ($n = 130$), we identified $n = 7$ professionals (5.4%) with increased low-grade inflammation (CRP $>$ 5 mg/L, yet no further known inflammation-associated medical conditions) and $n = 123$ (94.6%) with no respective indication (CRP $<$ 5 mg/L). Further, we observed a mean leukocyte count of $M = 6.88\ 10^9$/L (95% CI [6.66, 7.11]). Both inflammatory endpoints were associated: Leukocyte numbers differed significantly between groups with CRP $<$ 5 mg/L ($M = 6.81\ 10^9$/L, 95% CI [6.58, 7.04]) and CRP $>$ 5 mg/L ($M = 8.20\ 10^9$/L, 95% CI [7.13, 9.27]; $F(\text{df} = 1) = 7.95$, $p = .006$). In Table 1 individual, employment, and psychosocial work characteristics are presented for the total sample ($N = 140$) and both subgroups, respectively.

Associations between working conditions and low-grade inflammation

The results of the regression analyses on bivariate (crude) and multivariate (adjusted) associations between professionals' individual, employment, and psychosocial work characteristics with inflammatory outcomes (CRP and leukocytes) are depicted in Table 2.

Table 1. Care professionals' individual, employment, and psychosocial work characteristics (for overall group and subgroups based on CRP cut-off > 5mg/L).

Measures	Overall Group	Subgroups for Analyses		
		CRP > 5mg/L	CRP < 5mg/L	Oneway ANOVA
	N = 140	*n* = 7	*n* = 123	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	
Individual characteristics				
Age (in years)	44.10 (12.39)	46.43 (7.55)	44.35 (12.52)	$F(1, 128) = 0.19$, $p = .665$
Body mass index	25.63 (4.31)	28.45 (6.24)	25.29 (4.03)	$F(1, 128) = 3.80$, $p = .053$
Employment characteristics				
Weekly working time	37.21 (7.74)	40.00 (0.00)	37.12 (7.98)	$F(1, 126) = 0.78$, $p = .380$
Psychosocial work characteristics				
Work overload	3.20 (1.06)	3.52 (0.88)	3.12 (1.02)	$F(1, 128) = 1.03$, $p = .312$
Social support	3.06 (0.68)	3.07 (0.79)	3.07 (0.67)	$F(1, 127) = .00$, $p = .995$
Job autonomy	3.23 (1.06)	4.11 (0.67)	3.21 (1.03)	**$F(1, 128) = 5.12$, $p = .025$**

Note. $n = 10$ (of $N = 140$) participants were excluded from analysis due to acute or chronic inflammation-related medical conditions. *M* = Mean, *SD* = Standard deviation. Significance testing: ANOVA, bold if $p < .05$. Scale ranges of work overload and autonomy: 1 = 'no, not all' to 5 = 'yes, to a great extent'. Scale range of social support scale: 1 = 'not at all' to 4 = 'to a great extent'.

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Table 2. Crude and adjusted associations of care professionals' individual, employment, and psychosocial work characteristics with inflammatory markers (C-reactive protein and leukocytes).

		Associations with Outcome							
		C-reactive protein				Leukocytes			
		Crude		Adjusted		Crude		Adjusted	
	Predictors	OR (95% CI)	p-value	OR (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Individual characteristics	Sex (male / female)	1.77 (0.20, 15.31)	.605	1.37 (0.10, 18.12)	.812	0.38 (-0.16, 0.91)	.165	0.52 (-0.09, 1.12)	.093
	Age	1.01 (0.95, 1.08)	.663	1.02 (0.91, 1.14)	.717	0.00 (-0.02, 0.02)	.944	0.00 (-0.02, 0.02)	.899
	Body mass index	1.14 (0.99, 1.32)	.066	1.20 (0.97, 1.48)	.099	-0.01 (-0.06, 0.048)	.825	-0.02 (-0.07, 0.04)	.607
Employment characteristics	Shiftwork (no/yes)	0.39 (0.07, 2.27)	.293	0.59 (0.07, 5.33)	.638	0.02 (-0.57, 0.61)	.951	-0.24 (-0.89, 0.41)	.462
	Weekly working time (in h/w)	1.23 (0.66, 2.31)	.520	1.80 (0.46, 7.10)	.402	0.01 (-0.02, 0.04)	.419	0.02 (-0.01, 0.05)	.210
Psychosocial work characteristics	Work overload	1.55 (0.66, 3.60)	.313	2.29 (0.59, 8.96)	.233	0.08 (-0.15, 0.32)	.491	0.09 (-0.17, 0.35)	.494
	Social support	1.00 (0.46, 2.17)	.995	1.14 (0.37, 3.46)	.823	0.02 (-0.20, 0.25)	.835	0.11 (-0.15, 0.36)	.400
	Autonomy	**3.00 (1.08, 8.39)**	**.036**	**4.10 (1.10, 15.26)**	**.035**	-0.08 (-0.31, 0.15)	.474	-0.11 (-0.35, 0.14)	.402
Model fit		$R^2_N = 0.00–0.12$		$R^2_N = 0.32$		$R^2 = 0.00–0.02$		$R^2 = 0.04$	

Note. OR = Odds ratio; CI = Confidence interval; B = non-standardized regression coefficient, intercept values not depicted; R^2_N = Nagelkerke's R^2; **bold if $p < .05$**, $n = 130$.

Crude: bivariate regressions (one predictor variable at a time); adjusted: each predictor variable + all other listed variables (sex, age, body mass index, shiftwork, weekly working time, work overload, social support, autonomy)

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Concerning the likelihood of elevated CRP levels, the following associations between professionals' individual and work-related characteristics were observed: There was a weak association between BMI and CRP that was yet neither significant in bi- (crude OR = 1.14, 95% CI [0.99, 1.32], $p = .066$, $R^2_N = 0.07$) nor in multivariate analyses (adjusted OR = 1.20, 95% CI [0.97, 1.48], $p = .099$, $R^2_N = 0.32$). Furthermore, there was a relation between autonomy and CRP such that reports of high autonomy were associated with increased levels of CRP (crude OR = 3.00, 95% CI [1.08, 8.39], $p = .036$, $R^2_N = 0.12$; adjusted OR = 4.10, 95% CI [1.10, 15.26], $p = .035$, $R^2_N = 0.32$). However, following the Benjamini-Hochberg correction with a critical value of $p\left(\frac{1}{8} \times .05\right) = 0.0625$, it was not statistically significant. We also tested associations with different adjustment sets (i.e., adjusted for age, sex, BMI only and additionally for shiftwork and working time), what yielded similar results (S2 Table).

To test this observed statistical trend, further potential confounding variables were considered. We analyzed the following health-related characteristics and their association with CRP, respectively: CVD risk (no/yes; crude OR = 4.04, 95% CI [0.75, 21.68], $p = .103$), diabetes (no/yes; crude OR = 10.08, 95% CI [0.80, 127.42], $p = .074$), and current and past smoking (in pack years, crude OR = 1.02, 95% CI [0.94, 1.09], $p = .687$). We also deployed professional tenure (instead of age) as a proxy estimate for accumulated exposure to work stressors (crude OR = 1.04, 95% CI [0.97, 1.12], $p = .250$).

Adjustment for these potential confounders in the association between autonomy and CRP did not change the results, i.e., the potential effect of autonomy remained (although not statistically significant after correction for multiple testing). S3 Table reports the adjusted estimates for both outcomes, respectively. Additional control for regular physical activities in leisure time (analogous to Table 2) still showed a possible effect of autonomy on CRP (crude OR = 3.95, 95% CI [0.69, 22.53], $p = .122$, $R^2_N = 0.07$; adjusted OR = 8.09, 95% CI [1.26, 52.02], $p = .028$, $R^2_N = 0.42$).

To rule out potential alternative explanations (e.g., poor physical work environment) and to account for potential contextual influences, we further included professionals' reports on adverse environmental conditions in the workplace and physical demands in the models. In bivariate analyses, none of the scales was related to CRP levels (adverse environmental conditions: crude OR = 1.20, 95% CI [0.55, 2.62], $p = .648$; physical demands: crude OR = 0.80, 95% CI [0.38, 1.67], $p = .545$). Additional insertion of both scales, respectively, into the multivariate model revealed no significant relationships and did not change the above reported putative effect of job autonomy.

Given the low number of identified participants with increased low-grade inflammation, testing for potential interaction effects between the three job factors and participants' CRP levels (i.e., JDC-S model's buffer hypothesis) was undertaken for exploratory reasons only. We neither observed a significant association for the work overload x social support interaction (adjusted OR = 1.18, 95% CI [0.20, 6.79], $p = .857$) nor for the work overload x autonomy interaction (adjusted OR = 0.76, 95% CI [0.14, 4.14], $p = .753$).

Regarding our second outcome leukocyte count, we did not observe significant relationships between the study variables and professionals' leukocyte numbers neither in the crude nor adjusted models (see Table 2). Adjustment for further health-related variables (CVD risk, diabetes, smoking) did not change these results (see S3 Table). We also applied the logarithmic transformation to the leukocyte count outcome measures, that did not change the results either.

We additionally conducted a sensitivity analysis by repeating the main analyses with the full study sample ($N = 140$; i.e., without exclusion of participants with elevated inflammation due to acute or chronic medical conditions). Concerning CRP, results were similar for individual

and employment characteristics, yet there was no longer an association with autonomy, but instead a significant relationship with work overload. For leukocytes, the results were similar to the findings reported above (see S4 Table).

Discussion

Findings and potential contributions

Chronic work stress potentially leads to adverse changes in multiple biological systems including the immune system. An emerging research base argues for pathways between exposure to unfavorable workplace conditions and professionals' chronic systemic low-grade inflammation. However, respective investigations specifically for healthcare professionals are scarce. Drawing upon on an exploratory study into geriatric care professionals' work factors and inflammatory markers, our preliminary findings contribute to the current knowledge base in various ways.

First, a prevalence of 5.4% of care professionals with critically elevated CRP levels, which were not related to known medical conditions, was determined. Hence, our findings inform future investigations that seek to identify occupational risk groups for disease susceptibility. Follow-up studies are necessary to examine the likelihood of chronic diseases in care professionals with altered inflammatory markers and long-term stress exposure [12, 23, 32].

Second, our study deployed a well-established job-stress model to discern associations between care professionals' working conditions and inflammatory markers. The application of work stress models rather than aggregate measures and disparate constructs helps to gain a deeper understanding of the fundamental processes of job stress and ensuing dysregulated immune function [12, 45, 66]. Concerning the main propositions of the JDC model, we found no empirical confirmation for the health-impairment process, i.e., deleterious effects of work overload on inflammatory processes. However, we observed a low positive, yet non-significant association between work overload and CRP. Previous JDC-based investigations revealed inconsistent results regarding CRP often with none or weak associations [12, 19, 39, 40, 45, 46]. A meta-analysis on another well-established job-stress model (i.e., effort-reward imbalance, ERI) found an overall, yet small effect of ERI on immunity with stronger effects on mucosal immunity (salivary immunoglobulin A) than on cytokine including CRP as well as leukocyte subsystems [20]. Since the majority of research is based on non-nursing settings, definite inferences concerning the effects of overload on low-grade inflammation in care professionals are premature. Contextual conditions that mitigate the adverse effects of overwork in healthcare should be considered in future research, e.g., opportunities for respite and recovery in care professionals under high work demands [67]. Contrary to our assumptions, we found a tendential positive effect of job autonomy on participants' CRP levels. This observed trend deserves careful consideration in the light of the current literature and our applied methods. Traditionally, job autonomy has been considered as a fundamental resource for effective task regulation and as beneficial for health and mental well-being [42, 68, 69]. Notwithstanding, high levels of job autonomy have also been associated with poor health and well-being outcomes, also in eldercare professionals [70–73]. One post-hoc explanation for such detrimental effects may be that high job autonomy depletes self-regulatory efforts due to exceeding planning requirements, high demands for self-control, and decreased predictability of work tasks [71]. Our findings thus contribute to investigations into inverse or potentially curvilinear relationships between job autonomy and health outcomes [72, 74]. It has been suggested that physiological dysregulation with sympathetic activation and parasympathetic withdrawal occurs when high autonomy is perceived as an additional stressor [70]. Moreover, whether autonomy functions as a protective factor might depend on individual traits such as self-

efficacy [39], in that individuals with low levels may perceive a high degree of autonomy as overcharging and hence show stress reactions. Future investigations should thus scrutinize potential harmful effects of job autonomy on immunological processes.

Third, the associations were not uniform for both study outcomes. CRP is one of the most frequently studied inflammatory markers and is suggested to be positively associated with work stress [12]. In contrast, the study base on leukocytes is limited so far and findings show diverse or no associations with workplace stress, especially when assessed with the JDC(-S) model [12, 19]. Leukocytes as a marker of cellular immunity are expected to decrease in number in response to chronic stress [12]. Effects of workplace-related stress on leukocyte levels in particular need to be further investigated; in general, consideration of several molecular-biological (i.e., humoral, cellular, and intracellular) levels of the immune system in work stress research would be desirable and allow to discern potential confluent or disparate effects of job factors on different branches of the immune system.

We explored potential multiplicative effects according to the buffer hypothesis of the JDC-S model [63]. Despite the constraints of this survey (i.e., limited prevalence of low-grade inflammation), we tested for moderating effects to obtain further insights into possible interdependencies between the job factors in nursing. Our null findings are consistent with reviews suggesting that moderating influences of control and social support lack substantial empirical confirmation [63, 75, 76].

Limitations

Our observations should be interpreted in the light of important limitations. Firstly, we used a cross-sectional design what limits inferences on causality and long-term effects. In cross-sectional studies, the "level of chronicity" [12] of stress experience is often not considered, yet inflammation-related processes are suggested to vary in different stages of stress [77]. Although we have included important proxy variables such as professional tenure, the duration of job stress may not have been comparable in our sample with possible effects on the biomarkers. Future studies should consider the level of chronicity by collating multiple information including psychological symptoms, in order to differentiate between individuals in different phases of job stress—from acute stages up to burnout [9, 12]. Moreover, peripheral inflammation is modulated by other human stress systems through complex neuroendocrine-immune cascades and interactions, and should thus not be investigated in isolation in future research, but in its interplay with other stress markers, in particular the hypothalamus-pituitary adrenal axis hormone cortisol [78].

Our data stemmed from geriatric care professionals, who underwent a standardized, periodic health examination. This may limit generalizability to other nursing work environments. Yet, regularly scheduled examinations reduce the probability of self-selection bias. We acknowledge the unequal distribution of men and women what limits inferences concerning potential sex differences in (work) stress-related inflammatory responses [16, 41].

Furthermore, we are aware that for CRP different methods and cut-offs are used depending on the research subject or clinical indication. In our study, a cut-off of 5 mg/L was applied following our study's laboratory standard reporting procedure. In another study based on a healthy working sample a similar cut-off was deployed [79]. Yet, in several other studies, high-sensitivity CRP was used with lower detection limits [16, 18, 39], providing greater resolution in lower CRP-concentrations. In this regard, it is also noteworthy that we were restrictive in excluding participants with elevated CRP concentrations due to known medical reasons for inflammation. Future research should elaborate consistent methods for instance by defining clear thresholds and exclusion criteria for better comparability and replicability of findings.

The importance of this aspect was reflected in the results of our additional sensitivity analysis, which were different for CRP, when no exclusion criteria were applied. Indeed, it is crucial to thoroughly distinguish chronic systemic low-grade inflammation from reactions to infection or injury, in order to capture inflammation induced by *psychological* stress rather than by medical conditions [9, 80].

Moreover, although we controlled for a broad set of confounders, we acknowledge that further factors outside the work environment may influence the interplay of occupational conditions and immunological processes. Future investigations should strive to control for potentially amplifying but also protective functions of individual behaviors, personal characteristics, and social circumstances. For example, job strain in combination with caregiving to a relative was shown to have the strongest adverse effects on physiological functioning in civil servants [81]. On the other hand, regular and efficient sleep may mitigate inflammatory processes in nursing professionals [82]. Moreover, specific personal resources might be protective against adverse effects of work stress on immune function, as was shown for trait mindfulness among care workers [83]. Another limitation in this context is that we did not control for participants' respective profession due to confidentiality measures.

Finally, this exploratory study was based on a convenience sample with a limited number of participants. In the original study, we tried to recruit as many participants as possible through various measures. However, like in other applied biomarker studies, we faced the challenge of large exclusion rates of participants because of appointment cancellations (e.g., due to spontaneous shift changes, sick leave, holiday), medical reasons (e.g., specific medical or psychiatric conditions affecting blood levels), personal reasons (e.g., refusal to provide sample) or other reasons such as pregnancy. In view of the low prevalence of the outcome, our study was strongly underpowered and therefore, results can only be interpreted with great caution. Future studies ought to replicate observed effects with larger samples to achieve greater power. In addition, the results regarding social support in particular should be cautiously considered, as this measure showed low internal consistency, perhaps due to the limited number of merely two items.

Implications for research and nursing practice

Regarding further research, this study advocates the viability of inflammatory markers in the quest for work-related influences on care professionals' health. Yet, prospective studies on accumulated exposures to adverse working conditions and immunological status over time are necessary [19, 27]. Ensuing research should also consider the utility of other indicators of inflammation, e.g., cytokine imbalance as a composite measure of pro-inflammatory and anti-inflammatory expression [12]. Moreover, the application of a holistic approach, as per the allostatic load index, a multi-system indicator of wear-and tear effects on brain and body, may give deeper insights into how chronic work stress in nursing leads to different adverse health outcomes in the long-term [84–87]. Consequently, this may contribute to attempts to quantify current or future disease risks in nursing samples, for example with identification of immune-risk phenotypes [32]. Future studies should also examine the consistency of our observations by applying alternative job-stress models (such as ERI) and by including other job stressors, such as those specific to healthcare (i.e., caring for suffering patients), or organizational stressors, like job insecurity and experience of injustice [16, 27, 66]. Besides the traditional work stressors, also other, more severe stressors, such as workplace bullying or harassment, should be subjected to future research. Those kinds of stressors may be perceived as threatening to psychosocial safety and may elicit severe stress reactions in individuals [88]. Thus, the choice of exposure measures might affect the potential to capture work stress at a physiologically detectable level.

Concerning implications for nursing practice, our results underline the need for further measures to promote nurses' well-being and health. Given their high workload and intense demands, care professionals may constitute a vulnerable population. Since low-grade inflammation is suggested as a powerful predictor of chronic diseases [9–11], inflammatory markers may represent an important leverage point for identification of health status and potential need for action. For one thing, monitoring of inflammatory markers as indicators of dysregulated stress-physiological functioning in the course of standard medical examinations could help to identify at-risk professionals for detrimental health outcomes. For another thing, workplace interventions could be implemented to improve inflammatory processes: in healthcare professionals, meditation- and mindfulness-based trainings were shown to alter pro-inflammatory gene expression [89, 90]; across different occupational settings, physical activity interventions were demonstrated to decrease employees' CRP levels [19].

Conclusion

Chronic low-grade inflammation has become increasingly important for our understanding of the pathogenesis of (work) stress-related diseases. Taken together, this exploratory study provides valuable insights into potential biological correlates of psychosocial work stress in care professionals. Given the study's limitations, the findings are preliminary and their interpretation warrant caution. Further research is needed to clarify the role of job demands as well as resources for immune function in healthcare workers.

Supporting information

S1 Fig. Flow chart describing step-wise selection of study sample.
(TIF)

S1 Table. Comparison of excluded participants with study sample regarding sociodemographic and employment-related information.
(DOCX)

S2 Table. Crude and adjusted associations (including different adjustment sets, Model 1–3) of care professionals' individual, employment, and psychosocial work characteristics with C-reactive protein.
(DOCX)

S3 Table. Expanded list of care professionals' individual, employment, and psychosocial work characteristics and associations with inflammatory markers (C-reactive protein and leukocytes).
(DOCX)

S4 Table. Crude and adjusted associations of care professionals' individual, employment, and psychosocial work characteristics with inflammatory markers (C-reactive protein and leukocytes), full sample.
(DOCX)

Author Contributions

Conceptualization: Helena C. Kaltenegger, Matthias Weigl, Linda Becker, Nicolas Rohleder, Dennis Nowak, Caroline Quartucci.

Data curation: Matthias Weigl, Caroline Quartucci.

Formal analysis: Helena C. Kaltenegger, Matthias Weigl.

Investigation: Caroline Quartucci.

Methodology: Helena C. Kaltenegger, Matthias Weigl, Linda Becker, Nicolas Rohleder, Dennis Nowak.

Project administration: Matthias Weigl.

Supervision: Matthias Weigl.

Writing – original draft: Helena C. Kaltenegger.

Writing – review & editing: Helena C. Kaltenegger, Matthias Weigl, Linda Becker, Nicolas Rohleder, Dennis Nowak, Caroline Quartucci.

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2.4 Paper IV

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., Quartucci, C., & Weigl, M. (2023). Associations of technostressors at work with burnout symptoms and chronic low-grade inflammation: A cross-sectional analysis in hospital employees. *International Archives of Occupational and Environmental Health*, 1–18. https://doi.org/10.1007/s00420-023-01967-8

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ORIGINAL ARTICLE

Associations of technostressors at work with burnout symptoms and chronic low-grade inflammation: a cross-sectional analysis in hospital employees

Helena C. Kaltenegger[1] · Linda Becker[2] · Nicolas Rohleder[2] · Dennis Nowak[1] · Caroline Quartucci[1,3] · Matthias Weigl[1,4]

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Abstract

Objective Despite the increasing scholarly interest in the phenomenon *technostress,* associated biological effects on employee health are under-researched. Chronic low-grade inflammation is suggested as a central pathway linking stress experience to disease development. The aim of this study was to assess associations of technology-related work stressors (technostressors) with low-grade inflammation and burnout symptoms.

Methods $N = 173$ (74.6% women, $M_{age} = 31.0$ years) university hospital employees participated in a cross-sectional study. Self-report questionnaires were used for the assessment of general psychosocial working conditions (work overload, job control, social climate), a range of different technostressors, burnout symptoms, and relevant confounders. Participants provided capillary blood samples, and high-sensitivity C-reactive protein (hs-CRP) as an inflammatory biomarker was analyzed from dried blood spots.

Results Based on a factor analysis, we identified four underlying dimensions of technostressors: techno- and information overload, techno-complexity, interruptions and multitasking as well as usability and technical support. In multivariate linear regressions, techno-/information overload and techno-complexity were associated with core (exhaustion, mental distance) and secondary (psychosomatic complaints) symptoms of burnout. Techno-/information overload was a significant predictor of burnout core symptoms, even when general work overload was controlled for. The technostressors were not associated with hs-CRP.

Conclusion This is the first study on technology-related stress at work and chronic low-grade inflammation. The results suggest that (information) overload caused by digital technology use is a distinct work stressor with genuine consequences for psychological health. To what extent these effects also manifest on a physiological level needs to be subjected to future studies, ideally with prospective designs.

Keywords Burnout · C-reactive protein · Inflammation · Stress · Technostress · Work

Introduction

The advancing digitalization has pervasive consequences on the psychosocial work environment and thereby on workers' health and well-being (Dragano and Lunau 2020; Parker and Grote 2022). These can be negative in terms of stress experience and impaired mental health, but also positive for workers' health and well-being for instance due to greater flexibility in work organization, better access to information, or automation (Dragano and Lunau 2020; La Torre et al. 2019). Especially in healthcare, there have been fundamental advancements in terms of health information technology (e.g., electronic health records, computerized decision

✉ Helena C. Kaltenegger
helena.kaltenegger@med.lmu.de

1 Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstr. 1, 80336 Munich, Germany

2 Institute of Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

3 Bavarian Health and Food Safety Authority, Institute for Occupational Health and Product Safety, Environmental Health, Munich, Germany

4 Institute for Patient Safety, University Hospital Bonn, Bonn, Germany

support systems; Abbott and Weinger 2020). At the same time, healthcare professionals are already exposed to a high degree of work stress putting them at an increased risk for adverse health outcomes (Dawe et al. 2016; Adriaenssens et al. 2015; Kaltenegger et al. 2022).

Introduced by Brod in 1982, the definition of the phenomenon *technostress* changed over time with the latest referring to "stress experienced by end users of Information and Communication Technologies (ICTs)" (Ragu-Nathan et al. 2008, p. 417). Tarafdar et al. (2007) compiled technology-related factors that can cause technostress (*techno-overload*, *techno-invasion*, *techno-complexity*, *techno-insecurity*, *techno-uncertainty*), i.e., so-called technostressors (La Torre et al. 2019). Further technostressors include work interruptions by ICTs (Galluch et al. 2015; Ninaus et al. 2015), multitasking (Reinecke et al. 2017), or information overload (Eppler and Mengis 2004; Tarafdar et al. 2007). Existing reviews on technostress report strain reactions in employees related to psychological (e.g., burnout, exhaustion), physiological (e.g., activation of stress hormones), cognitive (e.g., concentration problems) and behavioral (e.g., job performance) symptoms (La Torre et al. 2019; Dragano and Lunau 2020; Berg-Beckhoff et al. 2017; Riedl 2012; Borle et al. 2021). However, these reviews also reveal that research on the health consequences of technostress is still fragmented and the evidence base is limited. In particular, the following knowledge gaps remain:

First, while it is well-researched that exposure to workplace stressors is associated with mental health problems (Madsen et al. 2017; Aronsson et al. 2017), studies on work stressors related to digital technologies and mental health outcomes are sparse with first results suggesting associations with burnout (Dragano and Lunau 2020). Burnout is defined as "a work-related state of exhaustion that occurs among employees, which is characterized by extreme tiredness, reduced ability to regulate cognitive and emotional processes, and mental distancing. These four core dimensions of burnout are accompanied by depressed mood as well as by non-specific psychological and psychosomatic complaints" (Schaufeli et al. 2020, p. 4). The few studies on technostress and burnout were predominantly based on office workers (Berg-Beckhoff et al. 2017). However, burnout is of critical concern especially in clinical work with implications not only for staffs' health but also for patient care and the entire healthcare system (Dall'Ora et al. 2020; West et al. 2018; Weigl 2022). Recent research in health professionals across different settings showed high to moderate levels of technostress and considerable associations with burnout symptoms amongst other health-related consequences (Golz et al. 2021; Kasemy et al. 2022). Specifically for electronic health record systems, current research among US physicians found that the usability was rated as poor and in turn, that perceived usability was related to provider task load and burnout with task load functioning as a mediator (Melnick et al. 2020a, b). Thus, more investigations on technostress and burnout in healthcare workers are needed.

Second, technostress has mostly been assessed with self-report questionnaires, while objectively measurable biological effects have largely been overlooked. Few studies suggest that technostressors activate physiological stress responses. This was shown for the sympathetic nervous system as one domain of the autonomic nervous system (ANS; e.g., Galluch et al. 2015) and the hypothalamic-pituitary-adrenocortical (HPA) axis (Riedl et al. 2012; Arnetz and Berg 1996; Kasemy et al. 2022). However, these findings relate to *acute* stress rather than to the long-term effects of *chronic* stress. As in modern digitalized work environments, technostressors may occur recurrently over prolonged periods, they might lead to chronic stress experience (Day et al. 2010). The human stress response includes—beyond the activation of the main stress systems (ANS and HPA axis)—complex effects of the immune system, most importantly up-regulation of inflammatory pathways (Ulrich-Lai and Herman 2009; Segerstrom and Miller 2004; Morey et al. 2015; Chrousos 2009). In the short-term, these changes are critical for survival, however, in the long-term, wear-and-tear effects of the stress systems can occur (cf. allostatic load model (McEwen 1998; McEwen and Stellar 1993))—as for instance the phenomenon of chronic systemic low-grade inflammation. Low-grade inflammation is suggested as a central pathophysiological mechanism in the development of chronic conditions encompassing cardiovascular, metabolic, and neurodegenerative diseases, depression as well as cancer (Couzin-Frankel 2010; Liu et al. 2017). It is usually assessed by measuring concentrations of the acute phase protein C-reactive protein (CRP) or of cytokines (such as interleukins) in blood or saliva (Rohleder 2019). Adverse psychosocial factors at work were associated with low-grade inflammation in employees, yet with limited evidence (Kaltenegger et al. 2021; Wright et al. 2020). For a better understanding of the long-term psychophysiological health effects of technostressors, it is essential to assess biomarkers indicative of biological alterations of the stress systems, such as chronic low-grade inflammation.

Third, it is unclear whether technostressors are genuinely new, distinct stressors or if they are just antecedents or specific forms of other general psychosocial work stressors like work overload or job insecurity (Dragano and Lunau 2020). Therefore, it is crucial to investigate technostressors in their interplay with other job characteristics and to test for individual as well as interactive effects. For example, technostress in terms of a system breakdown in a human–computer interaction task only increased the skin conductance of male participants if they were under time pressure (Riedl et al. 2013).

As a theoretical foundation, we use the well-established job demand-control(-support) (JDCS) model (Karasek 1979; Johnson and Hall 1988; Johnson et al. 1989): It proposes that the combination of high job demands, low job control, and low social support at work leads to mental strain, which is linked to cardiovascular disease (CVD) morbidity and mortality. Furthermore, we draw on the challenge-hindrance stressor framework (Cavanaugh et al. 2000; LePine et al. 2005; Podsakoff et al. 2007) that has been applied to the technostress concept (Califf and Sarker 2020; Tarafdar et al. 2019): Based on the notion of a duality of negative and positive sides of technology, technostressors can be divided into *hindrance technostressors* and *challenge technostressors*. Hindrance technostressors are technology characteristics appraised by the user as disturbing or threatening and comprise the aforementioned technostressors; challenge technostressors in contrast, are appraised as promoting task accomplishment and hence, alleviate technostress (Tarafdar et al. 2019; Califf and Sarker 2020). Several challenge technostressors have been proposed in the literature, such as *technical support provision* by solving users' ICT problems (Ragu-Nathan et al. 2008), and usability features consisting of *usefulness*, i.e., the degree to which technology improves job performance, as well as *reliability*, i.e., consistency and dependability of technology (Ayyagari et al. 2011).

In sum, we are only at the beginning of understanding the psychophysiological effects of technology-related stress at work—the research base is limited and there is a striking lack of studies on inflammatory (re-)activity as a major pathway in the transition to disease (Becker et al. 2022a, b; Kaltenegger et al. 2021). Therefore, this study sought to investigate associations of different risk factors at work, including technostressors and general psychosocial working conditions (job demands, control, social support), with burnout symptoms and low-grade inflammation among employees of a university hospital. In particular, we examined the following research questions:

(1) Are technostressors associated with burnout symptoms?
(2) Are technostressors associated with low-grade inflammation?
(3) If associations in (1) and (2) are significant, (3a) are they also existent, when controlling for general psychosocial work factors? (3b) are associations moderated by other technostressors or by general work factors (i.e., interaction effects)?

Methods

Design and ethics

This cross-sectional analysis is based on data collected in 2021 (June-November) as part of a larger cohort study on work stress and health sequelae in employees of the University Hospital of Ludwig-Maximilian University (LMU) Munich, Germany. The study protocol has been registered (for more information see: https://osf.io/94p6n/). The study was approved by the Ethics Committee at the Medical Faculty of LMU (20–0914) and is being performed in accordance with the ethical standards of the 1964 Helsinki Declaration. All participants included in the study provided written informed consent.

Participants

Persons undergoing an obligatory pre-employment medical examination at the Outpatient Clinic for Occupational, Social, and Environmental Medicine were invited to participate in the study. The sample thus consists of new employees at LMU University Hospital with different kinds of professions including nurses, physicians, (medical-) technical, research and administrative staff, etc. Prior to inclusion, participants received information concerning study objectives and procedures. Data collection took place on-site at the outpatient clinic in medical examination rooms. For this study, a subsample of $N = 173$ (74.6% women, $M_{age} = 31.0$ years) was analyzed consisting of participants who had already started their job or who had not started at that time, but who had been employed prior to the beginning of their employment at LMU University Hospital. The following eligibility criteria were applied: Persons with a temporary contract of less than six months were not included. Furthermore, persons reporting current symptoms indicating acute infection or inflammation (such as acute cold, fever, acute injuries, cystitis, etc.), permanent anti-inflammatory medication intake, recent intake of anti-coagulant drugs (last 12 h before testing), pregnancy, or insufficient German language knowledge were excluded. Participants with CRP levels > 10 mg/L were discarded a posteriori since concentrations above this cut-off suggest a medical source of infection or inflammation, what may bias the prediction of low-grade inflammation (Pearson et al. 2003).

Measures

Predictors

General psychosocial work factors A comprehensive questionnaire was developed for participants' self-report of their individual work situation. In line with the JDCS model, it included three scales for the assessment of psychosocial working conditions derived from a well-established tool for work analysis (Glaser et al. 2020): *Work overload* was measured with two items (item example: "I often have to hurry and still cannot complete my work"). Scale reliability was determined with Cronbach's $\alpha = 0.85$. *Job control* was

assessed with three items (e.g., "I can determine for myself how to do my work"; α = 0.86). *Social climate* was captured by two items (e.g.; "In this unit, work relationships with supervisors are based on trust"; α = 0.91). All items were answered on a five-point scale ranging from *not at all* to *to a very great extent*.

Technology-related work factors ("technostressors") For the measurement of work factors specifically related to digital technologies, we used 11 scales capturing a broad spectrum of potential technostressors:

For hindrance technostressors, four scales developed by Ragu-Nathan et al. (2008) (German translations based on Gimpel et al. (2018)) were applied: *techno-overload* (3 items; e.g., "I am forced by digital technologies to do more work than I can handle"; α = 0.84), *techno-complexity* (3 items; e.g., "I do not know enough about digital technologies to handle my job satisfactorily"; α = 0.87), *techno-uncertainty* (2 items; e.g., "There are always new developments in the digital technologies we use in our organization"; α = 0.75) and *techno-insecurity* (3 items; e.g., "I have to constantly update my skills on digital technologies to avoid being replaced"; α = 0.63). Further scales captured: *work interruptions* (3 items, adapted from Glaser et al. 2020; Büssing and Glaser 2002; e.g., "I often have to interrupt my work due to electronic messages [e.g., e-mail, device message]"; α = 0.70); *multitasking* requirements (2 items, adapted from Semmer et al. 1999; e.g., "Due to digital technologies I have to work on several tasks at the same time"; α = 0.90); and *information overload* (2 items, Piecha and Hacker 2020; e.g., "I feel that the information I receive via on-duty digital media is too much"; α = 0.93).

For challenge technostressors, the following scales were utilized: *reliability* (2 items, Ayyagari et al. 2011; Gimpel et al. 2018; e.g., "The digital technologies I use behave in a highly consistent way"; α = 0.90); *usefulness* (3 items, Ayyagari et al. 2011; Moore and Benbasat 1991; e.g., "Use of digital technologies improves the quality of my work"; α = 0.94); *involvement* (2 items, e.g.: "Our end users are consulted before the introduction of new digital technologies"; α = 0.79) and *technical support provision* (2 items, e.g.: "Our end-user help desk is easily accessible"; α = 0.89) (Ragu-Nathan et al. 2008; Gimpel et al. 2018).

Outcomes

Burnout (core and secondary symptoms) Burnout was measured using the German translation of the Burnout Assessment Tool (BAT) with the two scales core symptoms, consisting of the subscales exhaustion and mental distance, and secondary symptoms (Schaufeli et al. 2019; Glaser and Seubert 2020). The BAT was shown to have good psychometric properties (Schaufeli et al. 2020). Core symptoms were captured by two items per subscale; a sample item for exhaustion is "At work, I feel mentally exhausted", and for mental distance "I struggle to find any enthusiasm for my work". A total score for burnout core symptoms was calculated for each participant based on the mean of both subscales. The reliability for this scale was α = 0.79. Secondary symptoms, i.e., psychological and psychosomatic complaints, were assessed with six items; a sample item is "I suffer from headaches". For each participant, a mean score was computed. Scale reliability was α = 0.69. Answering options ranged from *never* to *always* on a five-point scale.

Low-grade inflammation: C-reactive protein We measured high-sensitivity C-reactive Protein (hs-CRP) in participants' capillary blood using the minimally invasive dried blood spot method (McDade et al. 2007). In short, blood drops from a prick into the participant's fingertip with a disposable lancet were collected on filter papers. The filter paper was dried at room temperature for at least 8 h and then stored in an envelope at −26 °C. Hs-CRP was analyzed with a "Human C-Reactive Protein/CRP Quantikine ELISA Kit" (IBL International) in the laboratory of the Chair of Health Psychology, Friedrich-Alexander University Erlangen-Nürnberg, in Nürnberg, Germany (Becker et al. 2022c for further details). The intra-assay coefficient of variation was 4.18%. Based on established cut-offs, values below 1.0 mg/L indicate a low, between 1.0 and 3.0 mg/L an average and above 3.0 mg/L a high risk for the development of cardiovascular diseases (e.g., Pearson et al. 2003).

Covariates

The following variables were assessed in the questionnaire as potential covariates:

Sociodemographic characteristics: sex (f/m/d), age (in years).

Health-related characteristics: body-mass index (BMI; kg/m^2), physical activity ("Overall, how much do you care about getting enough physical activity?", 1 = not at all – 5 = very much), smoking (no, former, current), alcohol intake ("How often do you have a drink containing alcohol, e.g., glass of wine, beer, cocktail, liquor or liqueur?"; dichotomized at ≥ 2–3 times a week; translated, Bush et al. 1998), chronic conditions (yes, no), hormone medication (for contraception and for other reasons; only for CRP).

Employment-related characteristics: Shiftwork (yes, no), night shift (yes, no), profession (nurse, physician, medical(-technical) personnel, research staff, administration, other), professional tenure (in years), full-time job (yes, no), leadership responsibility (yes, no), extended vacation during the previous 4 weeks before testing (≥ 3 weeks; yes, no), caring for COVID-19 patients (yes, no).

Statistical analyses

For the technostressor scales, first an exploratory factor analysis (Principal Component Analysis [PCA] with varimax rotation) was conducted to (1) explore the structure of the variables, (2) examine the validity of the items for the measurement of technostressors, and (3) reduce variables for the sake of parsimony and to limit multi-collinearity (Field 2009). For the retrieved factors, mean scores were calculated. Prior to performing parametric tests, measures were checked for normal distribution. Due to positive skewness, both burnout scales (core symptoms = 0.79; secondary symptoms = 0.70) and hs-CRP-values (= 2.81) were transformed using natural logarithm. All predictor variables were centered using grand mean centering. Cronbach's alpha (α) was calculated for the assessment of internal consistency.

After descriptive analyses, relevant confounders for burnout symptoms and CRP were identified using Pearson correlations, t-tests, and univariate variance analysis. For the analysis of our research questions, we applied linear regressions for each outcome: First, bivariate regressions for one control and one predictor variable at a time were calculated (crude model). Next, multivariate regressions for each predictor variable adjusted for all control variables were performed (model 1–7). Only control variables that showed significant associations with the outcomes in the first place were included in the regression models for reasons of parsimony. We applied the method of hierarchical regression with the identified covariates entered in the first step and each predictor (general work factors and technostressors) entered individually in the second step (research questions 1 and 2). Furthermore, in case of significant associations of technostressors with the outcomes, we additionally controlled for general psychosocial work factors (research question 3a), and if still significant, we tested for moderation effects of technostressors and general psychosocial work factors by including interaction terms into the multivariate models (research question 3b). Assumptions of regression analysis were checked using correlation matrices, variance inflation factor (VIF) values, Durbin-Watson test, histograms, and normal probability plots of residuals. Regarding multi-collinearity, correlations between predictors and covariates for the individual outcomes (burnout, core symptoms: $r \leq 0.55$; burnout, secondary symptoms: $r \leq 0.56$; CRP: $r \leq 0.30$) and VIF values (burnout, core symptoms: ≤ 1.56; burnout, secondary symptoms: ≤ 1.54; CRP: ≤ 1.17), indicated no too strong relationships (Field 2009). All statistical analyses were performed using SPSS Statistics version 26 (IBM SPSS Inc., Chicago, Il, USA).

Results

Factorial validity of technostressors

Bartlett-Test (Chi^2 (351) = 2925.67, $p < 0.001$) and Kaiser–Meyer–Olkin Measure of Sampling Adequacy (KMO = 0.83) indicated meritorious suitability of the variables for factor analysis (Kaiser 1970, 1974). The PCA revealed a six-factor-structure following the Kaiser criterion (Eigenvalue > 1). However, based on the scree-plot and theoretical as well as empirical considerations (Guadagnoli and Velicer 1988), we selected a four-factor solution explaining 61.3% of the total variance. Observed factors could be interpreted in line with the challenge-hindrance model: Factor I was classified as a challenge technostressor relating to usability characteristics and technical support provision (7 items, factor loadings: 0.59–0.88). The other three factors were conceptualized as hindrance technostressors: Factor II describes techno-overload and information overload due to digital technologies (5 items, factor loadings: 0.69–0.82); Factor III pertains to the complexity of digital technologies and associated perceived lack of skills (4 items, factor loadings: 0.72–0.87); and factor IV relates to work interruptions and multitasking demands in the context of digital technologies (5 items, factor loadings: 0.56–0.69). Items showing cross-loadings and/or loadings on a factor with only a few other variables were excluded from the analysis ($n = 6$ items). The factor loadings per item can be seen in Table S1 (Appendix). For the wording of the items, we refer to Ayyagari et al. (2011), Ragu-Nathan et al. (2008), and Gimpel et al. (2018) for German translations. The newly composed scales had high internal consistencies: α = 0.90 (factor I), α = 0.88 (factors II and III), and α = 0.84 (factor IV).

Descriptive statistics

Five participants were excluded from the analyses because of CRP > 10 mg/L ($n = 4$) or due to incomplete survey responses ($n = 1$). Further, one person of diverse gender had to be excluded, because group comparisons were not possible. The final sample size was $n = 167$. The sample consisted of 125 women (74.9%), the mean age was 31.1 years (standard deviation, $SD = 9.6$, range: 17–60), and the average BMI was 24.1 ($SD = 5.1$, range: 16.6–45.6). Most participants were nurses ($n = 46$, 27.5%), followed by physicians ($n = 33$, 19.8%), and research staff ($n = 30$, 18.0%). The remaining participants were medical-technical personnel (for labs, pharmacy, etc.; $n = 22$, 13.2%), administrative staff ($n = 10$, 6.0%), and other (such as therapists, midwives, nutritionists, social workers, etc.; $n = 24$, 14.4%). The majority was working full-time ($n = 129$, 77.2%), and 69 (41.3%) were working on a shift schedule with 57 participants doing night shifts.

Table 1 Descriptive statistics of covariates, predictor, and outcome variables

Covariates	*Mean (SD)*
Age, in years	31.1 (9.6)
BMI (kg/m^2)	24.1 (5.1)
Physical activity [1]	3.5 (1.0)
Professional tenure, in years	5.3 (7.7)
	Frequencies (%)
Smoking	
No	120 (71.9%)
Former	11 (6.6%)
Current	36 (21.6%)
Alcohol intake	
≤ 2–4 times per month	129 (77.2%)
≥ 2–3 times per week	36 (21.6%)
Chronic conditions (yes)	24 (14.4%)
Hormone medication, not for contraception (yes)	15 (9.0%)
Hormone medication, for contraception (yes)	24 (14.4%)
Predictors [2]	*Mean (SD)*
Work overload	2.58 (1.16)
Job control	2.95 (1.08)
Social climate	3.74 (1.21)
C-TS: Usability & technical support	3.36 (0.99)
H-TS: Techno- & information overload	2.16 (0.89)
H-TS: Techno-complexity	1.66 (0.73)
H-TS: Interruptions & multitasking	2.60 (1.02)
Outcomes	*Mean (SD)*
Burnout: core symptoms [3]	1.94 (0.74)
Burnout: secondary symptoms [3]	1.94 (0.57)
C-reactive Protein (mg/L)	1.23 (1.64)

C-TS challenge technostressor, *H-TS* hindrance technostressor

[1]Scale range: 1 = not at all – 5 = very much

[2]Scale range: 1 = not at all – 5 = to a very great extent

[3]Scale range: 1 = never – 5 = always

$N = 167$

Nineteen (11.4%) employees had leadership responsibilities and 26 (15.6%) were involved in the care of COVID-19 patients. Means and *SD*s as well as frequencies of all included variables are presented in Table 1.

Associations of work stressors with burnout (core and secondary symptoms)

Burnout core symptoms (exhaustion and mental distance) were significantly negatively associated with physical activity and longer vacations prior to testing (results not shown), and therefore, these variables were entered as covariates into the models. Results of the regression analyses on bivariate (crude) and multivariate (adjusted) associations of the covariates and predictors (general work factors and technostressors; models 1–11) with employees' burnout core symptoms are presented in Table 2. Work overload was a significant predictor of burnout symptoms (Model 1: non-standardized regression coefficient $B = 0.19$, $p < 0.001$). For job control and social climate, no significant associations were observed. However, for all three hindrance technostressors, there were significant positive relationships with burnout core symptoms in crude and adjusted models (techno-/information overload: Model 5: $B = 0.19$, $p < 0.001$; techno-complexity: Model 6: $B = 0.13$, $p < 0.001$; interruptions and multitasking: Model 7: $B = 0.12$, $p < 0.001$). Moreover, techno-/information overload remained a significant predictor of burnout, when general work overload was controlled for (Model 8: $B = 0.09$, $p = 0.005$). We also tested for potential moderation effects, but the interaction between work overload and techno-/information overload was not significant. Concerning the included covariates physical activity and prior vacation, robust negative associations with burnout core symptoms were observed in the crude and adjusted models (Table 2).

For burnout secondary symptoms, i.e., psychological and psychosomatic complaints, participants' sex, physical activity, smoking, and leadership responsibility were identified as relevant covariates. Results of the bivariate and multivariate regression analyses including these covariates, general work factors, and technostressors are depicted in Table 3. Again, work overload significantly predicted secondary symptoms (Model 1: $B = 0.05$, $p = 0.014$). Additionally, techno-/information overload (Model 5: $B = 0.07$, $p = 0.004$) and techno-complexity (Model 6: $B = 0.06$, $p = 0.038$) were significantly related to secondary burnout symptoms. However, when including general work overload in the models (model 8 and 9), associations of the technostressors were not statistically significant. As for the covariates, sex was a significant predictor of burnout secondary symptoms across all models, such that the female sex was associated with increased ratings. In addition, smoking was consistently a significant positive predictor for reporting secondary symptoms. On the contrary, there were trends across the models for negative associations between both physical activity (i.e., higher level of physical activity was associated with lower symptom ratings) and leadership responsibilities with secondary burnout symptoms (i.e., leaders reported less symptoms).

Associations of work stressors with low-grade inflammation (C-reactive protein)

Bivariate (crude) and multivariate (adjusted) regressions for the covariates, predictors (general and technostressors)

Table 2 Crude associations of control and predictor variables as well as adjusted associations of predictor variables with burnout (core symptoms)

		BAT core symptoms													
		Crude		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
		B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
Covariates	Physical activity*	**− 0.11**	**<.001**	**− 0.05**	**.034**	− 0.12	**<.001**	**− 0.12**	**<.001**	**− 0.12**	**<.001**	**− 0.08**	**.003**	**− 0.10**	**.001**
	Prior vacation (no, yes)	**− 0.19**	**.004**	− 0.05	.358	**− 0.17**	**.007**	**− 0.17**	**.006**	**− 0.18**	**.005**	**− 0.12**	**.033**	**− 0.16**	**.007**
Predictors:															
General work factors	Work overload	0.21	**<.001**	0.19	**<.001**										
	Job control	0.04	.118			0.05	.099								
	Social climate	0.02	.444					0.02	.425						
Techno-stressors	C-TS: usability & technical support	0.05	.089							0.04	.188				
	H-TS: techno-/ information overload	0.23	**<.001**									**0.19**	**<.001**		
	H-TS: techno-complexity	0.16	**<.001**											**0.13**	**<.001**
	H-TS: interruptions & multitasking	0.15	**<.001**												
	Work overload* information & techno-overload														
Model fit (R^2)		0.00–0.41		0.45		0.15		0.13		0.15		0.32		0.20	

Table 2 (continued)

		BAT core symptoms									
		Model 7		Model 8		Model 9		Model 10		Model 11	
		B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
Covariates	Physical activity*	**− 0.11**	**<.001**	**− 0.05**	**.047**	**− 0.05**	**.041**	**− 0.06**	**.030**	− 0.04	.099
	Prior vacation (no, yes)	**− 0.12**	**.044**	− 0.04	.434	− 0.05	.378	− 0.04	.469	− 0.03	.612
Predictors:											
General work factors	Work overload			**0.16**	**<.001**	**0.19**	**<.001**	**0.18**	**<.001**	**0.17**	**<.001**
	Job control										
	Social climate										
Techno-stressors	C-TS: usability & technical support										
	H-TS: techno-/ information overload			**0.09**	**.005**					**0.10**	**.002**
	H-TS: techno-complexity					0.03	.380				
	H-TS: interruptions & multitasking	**0.12**	**<.001**					0.03	.188		
	Work overload* information & techno-overload									− 0.04	.082
Model fit (R^2)		0.24		0.47		0.45		0.45		0.49	

B non-standardized regression coefficient, *C-TS* Challenge technostressor, *H-TS* Hindrance technostressor, *1 = not at all – 5 = very much; N = 167; bold if p < .05

Crude: bivariate regressions (one control and one predictor variable at a time)

Model 1: control variables + work overload

Model 2: control variables + job control

Model 3: control variables + social climate

Model 4: control variables + usability & technical support

Model 5: control variables + techno-/ information overload

Model 6: control variables + techno-complexity

Model 7: control variables + interruptions & multitasking

Model 8: control variables + work overload + techno-/ information overload

Model 9: control variables + work overload + techno-complexity

Model 10: control variables + work overload + interruptions & multitasking

Model 11: control variables + work overload + techno-/ information overload + work overload* techno-/ information overload

Table 3 Crude associations of control and predictor variables as well as adjusted associations of predictor variables with burnout (secondary symptoms)

		BAT secondary symptoms											
		Crude		Model 1		Model 2		Model 3		Model 4		Model 5	
		B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
Covariates	Sex (male, female)	**0.20**	**<.001**	**0.13**	**.011**	**0.14**	**.007**	**0.13**	**.011**	**0.13**	**.009**	**0.14**	**.007**
	Physical activity[1]	**− 0.07**	**.003**	− 0.04	.083	**− 0.06**	**.015**	**− 0.05**	**.017**	**− 0.06**	**.015**	− 0.04	.062
	Smoking (no, former, current)	**0.07**	**.010**	**0.05**	**.046**	**0.06**	**.027**	**0.05**	**.040**	**0.06**	**.027**	**0.06**	**.022**
	Leadership responsibility (no, yes)	**− 0.19**	**.008**	− 0.13	.050	− 0.13	.063	**− 0.14**	**.045**	− 0.13	.054	− 0.13	.058
Predictors													
General work factors	Work overload	**0.06**	**<.001**	**0.05**	**.014**								
	Job control	− 0.03	.108			− 0.03	.092						
	Social climate	**− 0.04**	**.032**					− 0.03	.067				
Techno-stressors	C-TS: usability & technical support	− 0.02	.344							− 0.02	.474		
	H-TS: techno-/ information overload	**0.08**	**.002**									**0.07**	**.004**
	H-TS: techno-complexity	**0.09**	**.003**										
	H-TS: interruptions & multitasking	0.01	.590										
Model fit (R^2)		0.00–0.10		0.20		0.18		0.18		0.17		0.21	

Table 3 (continued)

		BAT secondary symptoms							
		Model 6		Model 7		Model 8		Model 9	
		B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
Covariates	Sex (male, female)	**0.11**	**.037**	**0.13**	**.009**	**0.13**	**.008**	**0.11**	**.027**
	Physical activity[1]	**− 0.05**	**.035**	**− 0.05**	**.022**	− 0.04	.103	− 0.04	.094
	Smoking (no, former, current)	**0.06**	**.028**	**0.06**	**.023**	**0.05**	**.033**	**0.05**	**.044**
	Leadership responsibility (no, yes)	**− 0.15**	**.030**	**− 0.14**	**.036**	− 0.13	.059	**− 0.14**	**.040**
Predictors									
General work factors	Work overload					0.03	.266	0.04	.068
	Job control								
	Social climate								
Techno-stressors	C-TS: usability & technical support								
	H-TS: techno-/ information overload					0.05	.071		
	H-TS: techno-complexity	**0.06**	**.038**					0.04	.247
	H-TS: interruptions & multi-tasking			0.02	.282				
Model fit (R^2)		0.19		0.17		0.22		0.20	

B non-standardized regression coefficient, *C-TS* Challenge technostressor, *H-TS* Hindrance technostressor, *1 = not at all - 5 = very much; N = 167; bold if $p < .05$

Crude: bivariate regressions (one control and one predictor variable at a time)

Model 1: control variables + work overload

Model 2: control variables + job control

Model 3: control variables + social climate

Model 4: control variables + usability & technical support

Model 5: control variables + techno-/ information overload

Model 6: control variables + techno-complexity

Model 7: control variables + interruptions & multitasking

Model 8: control variables + work overload + techno-/ information overload

Model 9: control variables + work overload + techno-complexity

and hs-CRP are presented in Table 4. Regarding relevant covariates, age (only in the crude model), BMI, use of contraceptives, and leadership responsibility were consistently positively associated with employees' hs-CRP levels. Physical activity was negatively associated with hs-CRP (only in the crude model). For the predictors, results showed a statistical trend for a relation of work overload and hs-CRP (only in the crude model: $B = 0.15$, $p = 0.071$). For the other general work factors and the technostressors, no significant associations were observed neither in the crude nor in the adjusted models.

Discussion

The aim of this study was to assess associations of technostressors at work with psychological (i.e., burnout symptoms) and biological (i.e., hs-CRP as an inflammatory marker) health outcomes. To the best of our knowledge, this is the first study to investigate the potential effects of technostressors on immune activity in terms of chronic low-grade inflammation. Research on technostress as a risk factor for adverse psychophysiological health is still "work-in-progress" and there is a broad range of different theoretical terms and measures largely due to the interdisciplinary character of research on this phenomenon (Dragano and Lunau 2020, p. 411). With the ever-increasing digitalization and the ubiquity of digital technologies in employees' workplaces, it is timely to advance our understanding of the phenomenology of technostress and the consequences for employee health, both positive and negative.

To this end, our research approach comprised two steps: We measured technostress with a comprehensive questionnaire including 27 items from 11 scales based on the literature. In an attempt to identify underlying, latent dimensions within this compilation of variables, we first conducted an exploratory factor analysis (Field 2009). We extracted four factors and interpreted them in line with the challenge-hindrance model (Califf and Sarker 2020; Tarafdar et al. 2019). Factor I—the challenge technostressor "usability and technical support"—reflects the positive aspect of technostress, i.e., technology characteristics appraised as beneficial for work-related achievement (Podsakoff et al. 2007; Califf and Sarker 2020). This factor includes reliability of digital technologies, their usefulness for the execution of job tasks, and technical support provision at work. Factors II-IV represent hindrance technostressors, i.e., stressors appraised as thwarting job-related accomplishment (Podsakoff et al. 2007). Factor II ("techno- and information overload") can be interpreted as an extension of the well-established stressor techno-overload (Tarafdar et al. 2007), i.e., increased workload and work pace due to ICTs, by information overload, i.e., the feeling of too much information ("information flood") transmitted through ICTs (Piecha and Hacker 2020). Factor III ("techno-complexity and lack of skills") describes the users' feeling of inadequacy regarding their skills due to high complexity of ICTs requiring extra effort; this is accompanied by the feeling of pressure through coworkers with better ICT knowledge and skills (Tarafdar et al. 2007). And lastly, factor IV ("interruptions and multitasking") represents frequent interruptions of the workflow due to digital technologies and the requirement to perform several tasks simultaneously or alternately (i.e., multitasking) (Baethge and Rigotti 2013, 2010). As a second step, we investigated associations of these four factors with employees' burnout symptoms and low-grade inflammation under consideration of other job characteristics (work overload, control, social climate) and a broad range of potential confounders. Regarding our research questions, we yielded the following results:

First, we found associations of hindrance technostressors and burnout symptoms. In particular, techno-/information overload, techno-complexity as well as interruptions and multitasking were positively related to core symptoms of burnout. Moreover, techno-/information overload and techno-complexity were associated with secondary burnout symptoms. Our results thus add to the preliminary evidence for a positive association of technostressors and burnout (Dragano and Lunau 2020; Berg-Beckhoff et al. 2017). A prior study showed that high quantity and poor quality (i.e., high ambiguity) of workplace e-mail contributed to emotional exhaustion (Brown et al. 2014). E-mail stressors can be regarded as manifestations of our identified dimensions techno-/information overload, in terms of overstraining users' information-processing capacity (Eppler and Mengis 2004), and interruptions/multitasking by causing immediate interruptions of the workflow and the perceived requirement to perform several tasks simultaneously, in order to manage the amount of emails. Concerning techno-complexity, however, other studies did not find effects on burnout, but—similar to our results—effects of techno-overload and techno-insecurity (Califf and Brooks 2020; Day et al. 2012). With regard to secondary burnout symptoms, our observations are consistent with a previous investigation showing associations of telecommunication system engineers' perceived mental workload and lack of skills with psychosomatic symptoms such as headache, mental fatigue, or restlessness (Arnetz and Wiholm 1997). Altogether, our observations call for a more nuanced picture with potentially differential effects of distinct technostressors on various aspects of burnout.

Second, even after adjusting for work overload, techno-/information overload still significantly predicted burnout core symptoms and also secondary symptoms on a trend level. In contrast to previous studies (Califf and Sarker 2020; Ayyagari et al. 2011), we did not find any associations of

Table 4 Crude associations of control and predictor variables as well adjusted associations of predictor variables with C-reactive protein

		C-reactive protein															
		Crude		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
		B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*- value	B	*P*-value	B	*P*-value
Covariates	Age	**0.02**	**.044**	0.01	.315	0.01	.382	0.01	.347	0.01	.261	0.01	.303	0.01	.243	0.01	.316
	BMI	**0.10**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**	**0.11**	**<.001**
	Physical activity*	**−0.26**	**.012**	−0.12	.215	−0.15	.103	−0.15	.097	−0.17	.076	−0.16	.093	−0.17	.070	−0.16	.092
	Use of contraceptives (no, yes)	**0.80**	**.005**	**1.07**	**<.001**	**1.11**	**<.001**	**1.11**	**<.001**	**1.12**	**<.001**	**1.12**	**<.001**	**1.14**	**<.001**	**1.12**	**<.001**
	Leadership responsibility (no, yes)	**0.77**	**.015**	**0.55**	**.042**	0.51	.066	**0.54**	**.048**	**0.57**	**.040**	**0.55**	**.049**	0.54	.050	0.54	.052
Predictors:																	
General work factors	Work overload	0.15	.071	0.12	.136												
	Job control	0.05	.582			0.08	.318										
	Social climate	−0.09	.298					−0.06	.386								
Techno-stressors	C-TS: usability & technical support	−0.07	.508							−0.08	.386						
	H-TS: techno-/ information overload	0.08	.463									0.01	.928				
	H-TS: techno-complexity	0.04	.799											−0.09	.486		
	H-TS: interruptions and multitasking	0.13	.190													0.03	.707
Model fit (R^2)		0.00–0.16		0.29		0.28		0.28		0.29		0.28		0.29		0.28	

B non-standardized regression coefficient, *C-TS* challenge technostressor, *H-TS* hindrance technostressor, *1 = not at all - 5 = very much; bold if $p < .05$

Crude: bivariate regressions (one control and one predictor variable at a time)

Model 1: control variables + work overload

Model 2: control variables + job control

Model 3: control variables + social climate

Model 4: control variables + usability & technical support

Model 5: control variables + techno-/ information overload

Model 6: control variables + techno-complexity

Model 7: control variables + interruptions & multitasking

the challenge technostressor with our outcomes, i.e., no direct health-promoting effects. Nonetheless, we observed a small negative effect of social climate on secondary burnout symptoms, in that good social climate was related to fewer symptoms. Drawing upon the buffer hypothesis of the JDC model (Karasek 1979; van der Doef and Maes 1999), we sought to identify interaction effects between the job characteristics, i.e., whether job control, social climate or the challenge technostressor reduces the potential associations of work overload and the hindrance technostressors with the outcomes. We did not detect any interactions of technostressors and general work stressors. This is in line with a current review suggesting strong evidence for the absence of the theorized interaction effect between job demands and control in the prediction of workers' well-being (Huth and Chung-Yan 2022).

Third, we did not observe associations of technostressors with low-grade inflammation (hs-CRP). We just observed one, yet non-significant association of work overload in the crude model. This preliminary finding adds to the research base on the JDC(S) model and inflammatory markers, which heretofore is limited and inconclusive (Kaltenegger et al. 2021; Wright et al. 2020; Nakata 2012). Again, we could not identify any effects of job control and social climate on hs-CRP, whereas few previous investigations reported protective effects of job resources such as supervisor support (Eguchi et al. 2016), control (Shirom et al. 2008) or organizational justice (Elovainio et al. 2010) in terms of reduced inflammation. In hospital employees, respective investigations are sparse. One recent study surprisingly found a positive relationship of job autonomy and CRP among geriatric care professionals, perhaps due to greater responsibilities and experiences of excessive demands (Kaltenegger et al. 2022).

With regard to the included covariates, physical activity was consistently negatively associated with burnout symptoms and hs-CRP (significantly only in the crude model). While it is well-documented that physical activity during leisure time has beneficial effects on physical and mental health, occupational physical activity can be detrimental—a phenomenon called the physical activity health paradox (Holtermann et al. 2012; Lee et al. 2021). This aspect deserves careful consideration especially in the healthcare sector, where many professions face high physical demands such as lifting heavy loads, working in awkward postures, or walking long distances. Interestingly, participants in leadership positions had higher levels of CRP but reported less secondary burnout symptoms. Although higher occupational position has been associated with lower inflammation (e.g., Fraga et al. 2015), one can speculate that this small group of employees with leadership responsibilities at a large university hospital might be exposed to a particularly high work stress level and that confounding factors, such as profession, sex, age and professional tenure might explain this observation.

In sum, our results suggest that technostress in the form of techno- and information overload is associated with burnout symptoms. The association remained significant when work overload was included in the multivariate model. This finding indicates that (information) overload caused by digital technology use is a distinct work stressor with genuine consequences for psychological health. However, these might not be "strong" enough to manifest on a biological level in terms of chronic physiological activity, such as low-grade inflammation.

Limitations

Some important limitations need to be considered when interpreting our results. First, this study is cross-sectional and, therefore, no inferences concerning causality can be drawn. Second, based on the a-priori power analysis for the complete prospective cohort study yielding a required sample size of $N = 200$, our sample size may be regarded as too small and hence, our study might have been underpowered. However, as this sample consists of new employees, for a valid assessment of their work situation and associated influences, we rigorously had to exclude a large amount of the original sample. Participants who had not started their job at the university hospital at the time of examination and who were not working prior to the start of employment (because of studies/school, parental leave, unemployment or similar) were not included. Nonetheless, the heterogeneity in participants' life and work situations remains a critical issue. Therefore, we sought to control for potentially influencing factors, such as professional tenure and long vacation or leave in the weeks before testing. Due to the specific sampling procedure and the strict exclusion criteria, our sample consisted mainly of healthy participants of rather young age and short professional tenure, potentially resulting in a floor effect in terms of chronic stress experience. This might explain the comparatively low values in the burnout scales. However, the mean hs-CRP level was in the range of average risk for cardiovascular disease (Pearson et al. 2003). Participants' age might have also played a role in the evaluation of technostressors, as age has been identified as an important moderator (Reinecke et al. 2017; Tams et al. 2014). In sum, our recruitment method (i.e., pre-employment medical check) may have introduced bias concerning the sample and associations. The cohort was younger compared to the average healthcare worker, what might limit the external validity of our results. We checked for associations of participants' professions with the outcomes and did not find any significant differences. Therefore, we did not include profession as a covariate in our analyses. It can be assumed that most

of the jobs at this large university hospital were affected by the ever-increasing computerization, both in direct (such as medical care) and indirect clinical work (such as administration and research). Nonetheless, different professions might have been affected differently by technology exposure and inherent technostressors. Future research should hence distinguish between professional groups more clearly, in order to identify groups at particular risk for technostress, for instance due to a lack of digital competence (Golz et al. 2021). Further limitations pertain to the measurement of our outcomes: Burnout core symptoms were measured with only two subscales of the BAT with just few items; only hs-CRP concentrations were utilized as an inflammatory marker, while there a many other indicators of low-grade inflammation, such as cytokines (Kaltenegger et al. 2020, for a list). Although we collected broad screening information, we acknowledge that several, potentially confounding lifestyle and behavioral factors were not measured in sufficient detail, such as step count or weight change. Moreover, the inclusion of additional biomarkers of other stress systems, such as ANS (e.g., heart rate [variability]) and HPA-axis (e.g., cortisol), would be promising for a more comprehensive picture and deeper understanding of the linkage of (techno-)stress, biomarkers and burnout.

Implications for further research and occupational practice

Given that research on psychophysiological effects of technostressors is scarce, our results should be considered preliminary until further investigations can replicate them. Nonetheless, our study provides valuable methodological implications for future research. In particular, we suggest the following avenues with regard to design, measures, and samples: First, prospective studies are needed for a deeper understanding of dynamic and causal processes. Full-panel designs where each predictor and outcome variable is assessed at all measurement time points are suitable to identify both normal (i.e., stressor-to-strain) and reversed (i.e., strain-to-stressor) effects (Taris and Kompier 2014). Second, our operationalization of technostressors and the four-factor-structure should be scrutinized in future studies, and beyond the commonly studied negative aspects of technostress (i.e., hindrance technostressors), also positive (i.e., challenge technostressors) should be taken into account. Moreover, it is crucial to apply multiple methods, i.e., a combination of self-report data with measurable markers for biological stress, especially for chronic stress given its key role in long-term health. There is a long-standing debate on viable approaches to measure work-related stress (Semmer et al. 2003). The inclusion of biomarkers as outcome variables overcomes the problem of common method variance when both predictor and outcome variables are measured with self-report (Semmer et al. 2003). Moreover, self-report can be biased by individual response tendencies, whereas physiological data are less easily influenced by the participant or the examiners' expectations. However, also biomarkers have been discussed regarding conceptual, such as ambiguities in interpretation, as well as methodological issues, including limited reliability and potential confounding influences. Thus, self-report should not just be replaced—instead for an optimal assessment of psychobiological effects of work stress, a combination of various methods and multiple information sources is desirable (Semmer et al. 2003). Lastly, more research on technostress in hospital employees is necessary against the backdrop of the vast implementation of health information technology in hospitals.

For occupational health and safety management, there have been calls to consider job stressors related to the digitalization of work in the psychosocial risk assessment (Diebig et al. 2018; Chiappetta 2017). This will facilitate effective prevention and intervention measures on an organizational/structural as well as individual/behavioral level. Several strategies to cope with technostress have been described by healthcare managers, referring to establishing norms, such as good email culture, individual resources, such as digital literacy, and organizational resources, such as accessible and efficient IT support (Stadin et al. 2020). However, there is a lack of systematic prevention and intervention studies on work-related technostress (Rohwer et al. 2022). In general, workplace physical exercise interventions have been proven useful in the reduction of low-grade inflammation (Kaltenegger et al. 2021) and burnout (i.e., exhaustion) (Naczenski et al. 2017).

Conclusions

To the best of our knowledge, this is the first study on technology-related stress at work and chronic low-grade inflammation. Low-grade inflammation is a key pathway through which stress "gets under the skin" and ultimately affects humans' health. However, biological effects of technostress have been under-researched. We did not find associations of technostressors with inflammation, but techno- and information overload was consistently associated with burnout symptoms in employees of a university hospital. Nevertheless, due to peculiarities of our sample we cannot negate additional biological effects of this stressor in general and deem future research on this question as highly necessary.

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Author contributions *Conceptualization*: Helena C. Kaltenegger, Linda Becker, Nicolas Rohleder, Dennis Nowak, Caroline Quartucci, Matthias Weigl. *Data curation*: Helena C. Kaltenegger, Matthias Weigl. *Formal analysis*: Helena C. Kaltenegger, Matthias Weigl. *Investigation*:

Helena C. Kaltenegger, Caroline Quartucci. *Methodology*: Helena C. Kaltenegger, Linda Becker, Nicolas Rohleder, Dennis. Nowak, Matthias Weigl. *Project administration:* Matthias Weigl, Helena C. Kaltenegger. *Supervision:* Matthias Weigl. *Writing – original draft*: Helena C. Kaltenegger. *Writing – review & editing*: Helena C. Kaltenegger, Linda Becker, Nicolas Rohleder, Dennis Nowak, Caroline Quartucci, Matthias Weigl.

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Data availability The dataset generated during and/or analyzed during the current study are not publicly available due to them containing information that could compromise research participant privacy/consent. Public data availability was not considered in the application for ethical approval. However, upon reasonable request data are available from the corresponding author (HK).

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee at the Medical Faculty of Ludwig Maximilian University (LMU) Munich (November 23th 2020/ 20–0914). Informed consent was obtained from all individual participants included in the study.

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2.5 Paper V

Kaltenegger, H. C., Marques, M. D., Becker, L., Rohleder, N., Nowak, D., Wright, B. J., & Weigl, M. (2024). Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation. *Brain, Behavior, and Immunity.* Advance online publication. https://doi.org/10.1016/j.bbi.2024.01.222

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Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation

Helena C. Kaltenegger [a,*], Mathew D. Marques [b], Linda Becker [c,d], Nicolas Rohleder [c], Dennis Nowak [a], Bradley J. Wright [b,1], Matthias Weigl [a,e,1]

[a] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany
[b] School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia
[c] Institute of Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[d] Humanwissenschaftliche Fakultät, Vinzenz Pallotti University gGmbH, Vallendar, Germany
[e] Institute for Patient Safety, University Hospital Bonn, Bonn, Germany

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ABSTRACT

Background: Working conditions in the age of digitalization harbor risks for chronic stress and burnout. However, real-world investigations into biological effects of technostress, that is stress in the context of digital technology use, are sparse. This study prospectively assessed associations between technostress, general work stress, burnout symptoms, hair cortisol, and chronic low-grade inflammation.

Methods: Hospital employees (N = 238, 182 females, M_{age} = 28.5 years) participated in a prospective cohort study with two follow-ups six months apart (T2, T3). Participants answered standardized questionnaires on general job strain (job demand-control ratio), technostressors (work interruptions, multitasking, information overload), burnout symptoms (exhaustion, mental distance), and relevant confounders. Moreover, they provided capillary blood samples for C-reactive protein (CRP) and hair strands for hair cortisol concentration (HCC) analysis. Structural equation modelling was performed.

Results: The factorial structure of survey measures was confirmed. Burnout symptoms (M_{T2} = 2.17, M_{T3} = 2.33) and HCC (M_{T2} = 4.79, M_{T3} = 9.56; pg/mg) increased over time, CRP did not (M_{T2} = 1.15, M_{T3} = 1.21; mg/L). Adjusted path models showed that technostress was negatively associated with HCC (β = −0.16, p =.003), but not with burnout and CRP. General work stress in contrast, was not significantly associated with burnout, HCC or CRP. Furthermore, there were reciprocal effects of CRP on HCC (β = 0.28, p =.001) and of HCC on CRP (β = −0.10, p ≤.001). Associations were robust in additional analyses including further confounders.

Conclusion: This is the first study on prospective effects of technostress on employees' endocrine and inflammatory systems. Results suggest differential effects of technostress on the hypothalamic-pituitary-adrenocortical axis activity. Given its key role for long-term health, the findings have important implications for occupational health and safety in digitalized work environments.

1. Introduction

Stress is a major risk factor for the development of non-communicable diseases, like cardiovascular diseases, cancer or diabetes, which are the leading cause of death worldwide (WHO, 2022). The workplace can be stressful and substantially influence employees' health. There is ample evidence of the link of work stress with physical and mental morbidity as well as mortality (e.g., Kivimäki et al., 2012; Madsen et al., 2017; Taouk et al., 2020). In the light of the profound transformation of the world of work in the age of digitalization, new forms of work-related stress emerge, that is technostress (Brod, 1982) or digital stress (Hefner and Vorderer, 2016; Reinecke et al., 2017; Weinstein and Selman, 2016). The more commonly used term technostress can be defined as "stress experienced by end users of Information and Communication Technologies (ICTs)" (Ragu-Nathan et al., 2008). In modern work environments relevant and common technostressors are

* Corresponding author at: Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstr. 1, 80336 Munich, Germany.
E-mail address: helena.kaltenegger@med.uni-muenchen.de (H.C. Kaltenegger).
[1] Shared senior authorship.

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work interruptions, multitasking, and information overload due to ICTs (Eppler and Mengis, 2004; Galluch et al., 2015; Hefner and Vorderer, 2016; Reinecke et al., 2017). Technostress has been associated with different negative consequences regarding well-being, (mental) health, and work-related outcomes in employees (Dragano and Lunau, 2020; La Torre et al., 2019). However, technostress has mostly been assessed with self-report, while objectively measurable physiological effects of technostress are under-researched. The few existing studies on physiological stress responses focus on acute stress assessed in laboratory experiments rather than chronic stress related to ICT use in real-world settings (Becker et al., 2022a; Dragano and Lunau, 2020).

One important biological mechanism that explains how chronic stress, like work stress, "gets under the skin" is the hypothalamic pituitary-adrenocortical (HPA) axis with its main effector hormone cortisol. Chronic stress has been associated both with an increase in cortisol secretion (i.e. hypercortisolism), but also with a deficiency of cortisol (i.e. hypocortisolism) depending on a range of factors, such as stressor and person characteristics (Heim et al., 2000; Miller et al., 2007). Analysis of hair cortisol concentration (HCC) is increasingly used to measure long-term integrated cortisol levels retrospectively and as an indicator for chronic stress confers substantial advantages over the use of traditional fluid-based biomarkers such as salivary cortisol, as it is less influenced by biological rhythms or acute influences (Stalder et al., 2017).

Besides the HPA-axis, stress also has complex effects on the immune system with up-regulation of some parts, primarily inflammatory pathways, and down-regulation of others, primarily cellular immunity (Chrousos, 2009; Segerstrom and Miller, 2004). While inflammation is an adaptive reaction in the short-term, sustained low-grade inflammation is involved in the development of severe chronic diseases encompassing cardiovascular, metabolic, and neurodegenerative diseases, cancer as well as depression (Couzin-Frankel, 2010; Morey et al., 2015; Slavich and Irwin, 2014). Chronic systemic low-grade inflammation can be triggered by psychological stress alone without any apparent medical source (e.g., infection or injury) and can be measured with a range of biomarkers, such as the acute-phase-protein C-reactive protein (CRP) or cytokines (Black, 2002; Rohleder, 2019). Inflammation and abnormalities in cortisol secretion have been found to co-occur in clinical samples (i.e., depression), presumably due to glucocorticoid resistance, that is, a dysfunction of the glucocorticoid receptor leading to an impaired negative feedback loop of the HPA-axis (Pariante, 2017).

Available research on work-related stress and HCC is limited with inconsistent results, and there is a lack of prospective studies (Schaafsma et al., 2021). Furthermore, work stress has been associated with low-grade inflammation, but high-level evidence is weak due to a paucity of prospective research (Kaltenegger et al., 2021; Wright et al., 2020). Regarding technostress in particular, chronic effects on the two key biological mechanisms – the HPA-axis and chronic low-grade inflammation – have largely been overlooked. To our knowledge, two recent cross-sectional studies from our work group assessed for the first time, inflammatory responses to different technostressors without finding stress-induced increases (Becker et al., 2023; Kaltenegger et al., 2023).

One key mental health outcome in occupational health research is burnout. Burnout is suggested to develop as a consequence of chronic exposure to work stress and is expected to be associated with depletion of the HPA-axis, that is hypocortisolism (Miller et al., 2007; Rohleder, 2018). However, this notion has not been consistently supported empirically with recent studies reporting *increased* HCC in burned-out individuals (Penz et al., 2018; Wendsche et al., 2020). Besides alterations in the HPA-axis, increased systemic inflammation has been shown in burnout – yet the current evidence is inconclusive (Hänsel et al., 2010; Rohleder, 2019). Initial findings suggest associations of technostress with burnout, which are, however, mainly based on cross-sectional designs (Dragano and Lunau, 2020). In a prior study, specific forms of technostress (e.g., technology and information overload) were related to employees' burnout symptoms, even after controlling for general work overload (Kaltenegger et al., 2023). In sum, prospective research on technostress and burnout, as well as on the biological underpinnings of technostress and work stress in general, is limited. This highlights the need for advanced methods to gain a deeper understanding of potential health risks in modern working environments. Longitudinal designs, in which the same variables are assessed repeatedly over time in the same participants (i.e., full panel designs), provide an avenue to test the temporal order and direction of effects and best determine (reciprocal or reverse) causality (Ployhart and Vandenberg, 2010; Taris and Kompier, 2014).

Technostress may be especially relevant in healthcare settings, where health information technology is increasingly implemented, such as electronic health records or clinical decision support systems. Healthcare professionals are suggested to be an at-risk population for stress-related biological perturbations and development of burnout (Dawe et al., 2016; Maslach, 2003). Firstly defined by the psychologist Craig Brod (1982), the concept of technostress and its measurement was primarily developed in the discipline of information systems (e.g., Ayyagari et al., 2011; Ragu-Nathan et al., 2008; Tarafdar et al., 2007), but in recent years, it has also been applied to the healthcare context: For instance, Califf and Sarker (2020) found that negatively perceived technostress was associated with psychological distress in nurses, which in turn was related to low job satisfaction and high attrition, both impacting turnover intentions – a highly relevant issue in nursing. This was supported by a further study among health professionals in psychiatric hospitals, which also showed that technostress was associated with negative health consequences including burnout symptoms (Golz et al., 2021). Furthermore, in a recent cross-sectional study, university medical staff members and students reported moderate-to-high levels of technostress, which was positively associated with burnout and serum cortisol (Kasemy et al., 2022). Taken together, the emerging evidence suggests that technostress is an important phenomenon for different medical personnel, but in-depth research utilizing prospective designs is necessary.

To shed light into the possible associations of work stress, including technostress, burnout, HCC, and chronic low-grade inflammation, we conducted – to our knowledge for the first time – a prospective study with a full panel design among employees of a university hospital. As a conceptual framework, we drew upon the well-established job demand-control (JDC) model, which postulates that job strain results from a combination of high job demands and low job control (Karasek, 1979). The objective was to investigate general work stress (based on the JDC model) and technostress (work interruptions, multitasking, information overload) as predictors and burnout symptoms, HCC, and inflammation (CRP) as outcomes. In particular, we examined prospective associations of the predictors with the outcomes (research question 1) and prospective associations between the outcomes in order to identify their temporal order (research question 2).

2. Materials and methods

2.1. Design

A prospective cohort study at a large university hospital in South Germany with a full cross-lagged panel design including three measurement time points with a time lag of 6 months was conducted. Data collection took place from 06/2021 until 11/2022 with baseline

measurement (T1) from 06–11/2021,[2] first follow-up (T2) from 11/2021–05/2022, and second follow-up (T3) from 06–11/2022. The study was approved by the faculty's ethics committee (20–0914) and was carried out in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was registered (https://osf.io/94p6n/). All participants gave their written informed consent.

2.2. Participants and procedure

New hospital employees were recruited for study participation after their obligatory pre-employment medical examination. As an incentive, participants were compensated monetarily (€ 50) for study participation (i.e., for completing at least two measurement time points) and were provided with a personal report on their results (i.e., biomarker levels and scores in psychological constructs) after study completion. Prior to data collection, we performed an a-priori power analysis for bivariate linear regression based on an alpha of 0.05, a power of 0.80, and a small to medium effect size ($\beta = 0.18$), revealing a required sample size of $N = 187$ (Faul et al., 2007). A total of $N = 301$ participants were included in the study at baseline (T1), of whom $n = 241$ participated at follow-up I, 6 months later (T2), and $n = 200$ at follow-up II, 12 months later (T3). For follow-up measurements, participants were contacted by the study team following a standardized and iterative procedure, and an individual appointment for each participant at the clinic was arranged. The sample consisted of healthcare personnel with various professions, such as physicians and nurses, but also research staff and other.

Before inclusion in the study and each follow-up, we checked participants' eligibility with a screening on the following exclusion criteria: temporary contract of <six months (only T1), current acute disease symptoms (like acute cold or influenza-like infection, fever, cystitis, influenza, acute injuries, etc.), pregnancy, permanent intake of anti-inflammatory medication (e.g., cortisone, hydrocortisone), intake of anti-coagulant drugs in the last 12hr, and insufficient German language skills. A posteriori, we excluded participants, who dropped out after T1 ($n = 55$), who had extreme HCC levels (i.e., > 3 standard deviations [SD] from the mean across waves, $n = 2$), CRP levels >10 mg/L (Pearson et al., 2003) at any measurement time point ($n = 5$), as well as non-binary sex ($n = 1$).

2.3. Measures

A combination of standardized questionnaires for self-report and biomarker measurements was used. All variables were measured at each time point, except for sociodemographic information, profession, and body-mass index [BMI] (only at T1). The reliability of self-report measures was assessed by computing the Spearman-Brown statistic (ρ) for two-item scales and Cronbach's alpha (α) as well as McDonald's omega (ω) for scales with more than two items (Eisinga et al., 2013; Hayes and Coutts, 2020).

2.3.1. Self-report measures

2.3.1.1. General work stress. Based on the JDC model (Karasek, 1979), general work stress was measured with two scales derived from a well-established screening for psychological stressors at work (Glaser et al., 2020). *Job demands* was assessed with two items. A sample item is "I often have to hurry and still cannot complete my work". Reliability was acceptable, with ρ = 0.80 (T2) and ρ = 0.78 (T3). *Job control* was measured with three items (e.g., "I can determine for myself how to do my work"; α/ ω = 0.82 [T2], α = 0.82/ ω = 0.83 [T3]). Response options ranged from 1 = *not at all* to 5 = *to a very great extent*. A score was calculated by summing the item scores for each scale. Because of the difference in the number of items per measure, job demands (multiplied by 10) and control (multiplied by 20/3) were weighted to obtain values between 0 and 100 (Piantella et al., 2021). We then calculated the *job demand/control (JDC) ratio*, a continuous measure for job strain, where higher scores indicate higher job strain (e.g., Theorell et al., 1990). Moreover, means for job demands and control, respectively, were computed.

2.3.1.2. Technostress. For the assessment of work stressors specifically related to the use of digital technologies, three scales were used. *Work interruptions* were measured with three items (adapted from Büssing and Glaser, 2002; Glaser et al., 2020). A sample item is "I often have to interrupt my work due to electronic messages (e.g., e-mail, device message)". *Multitasking* was captured with two items (adapted from Semmer et al., 1999), such as "Due to digital technologies I have to work on several tasks at the same time". *Information overload* was also assessed with two items (Piecha and Hacker, 2020), such as "I feel that the information I receive via on-duty digital media is too much". Items were answered on a five-point scale (1 = *not at all* to 5 = *to a very great extent*). Individual scale means and an overall mean based on the three scales were calculated. The scale reliability for the overall mean was α = 0.84/ ω = 0.83 (T2) and α/ ω = 0.86 (T3).

2.3.1.3. Burnout symptoms. Burnout symptoms were measured with the Burnout Assessment Tool (BAT; Schaufeli et al., 2019; German translation: Glaser and Seubert, 2020). We used the two subscales *exhaustion* and *mental distance* with two items each. A sample item for *exhaustion* is "After a day at work, I find it hard to recover my energy" and for *mental distance* "I struggle to find any enthusiasm for my work". Possible responses ranged from 1 = *never* to 5 = *always* on a five-point scale. Individual subscale and a total mean for burnout symptoms were computed. Reliability for the total mean was α/ ω = 0.77 (T2) and α/ ω = 0.81 (T3).

2.3.1.4. Control variables. The following variables were assessed as potential confounders as suggested by previous research (de Hert, 2020; Magnusson Hanson et al., 2019; Meredith et al., 2022; Segerstrom and Miller, 2004; Stalder et al., 2017):

Sociodemographic characteristics: sex (f/m/d), age (in years);

Health-related characteristics: BMI (kg/m^2), physical activity ("Overall, how much do you care about getting enough physical activity?"; 1 = *not at all* to 5 = *very much*), smoking (1 = *never smoked* to 5 = *yes, every day*), hormone medication (for contraception and for other reasons);

Employment-related characteristics: profession (nurse, physician, medical [-technical] personnel, research staff, administration, other), shift work (yes/no), full-time job (yes/no);

Hair-related information: hair dyeing (including coloring, bleaching, henna, highlighting; all: yes/no), hair treatment (perm, straightening; both: yes/no), weekly hair washing frequency;

Procedural information: To account for potential seasonal variations of biomarker levels, the date of sampling was used to calculate variables reflecting the respective season. For HCC analyses, consistent with a previous study (Abell et al., 2016), a variable with eight categories was created including the four seasons (meteorological, northern hemisphere) and four overlapping seasons reflecting HCC levels in the four weeks prior to sampling (1 = spring/summer [June], 2 = summer [July, August], 3 = summer/autumn [September], 4 = autumn [October, November], 5 = autumn/winter [December], 6 = winter [January, February], 7 = winter/spring [March], 8 = spring [April, May]). For CRP analyses, a four-category variable was generated representing the

[2] Based on the data from T1 one previous study has been published (Kaltenegger et al., 2023). This was a cross-sectional analysis among a subsample of employees on associations between an extended set of technostressors (and general psychosocial work factors) with burnout symptoms and C-reactive protein. In contrast, this prospective study uses data from the whole cohort and two follow-up measurements and includes an additionally relevant physiological outcome (i.e., hair cortisol).

four seasons (1 = summer [June, July, August], 2 = autumn [September, October, November], 3 = winter [December, January, February], 4 = spring [March, April, May]).

2.3.2. Biomarkers

2.3.2.1. Hair cortisol concentration (HCC). Hair sample collection was optional for participants and was conducted only after additional informed consent was obtained. In each wave, >80 % of participants provided a hair sample with $n = 251$ at T1, $n = 201$ at T2, and $n = 161$ at T3. Hair strands were taken from the posterior vertex region of the head, tied off with a thin rubber band, and cut as close as possible to the scalp with specific scissors by a trained member of the study team. Subsequently, samples were enveloped in aluminum foil and stored in a box at room temperature. HCC was analyzed in the 1 cm segment of the hair strand most proximal to the scalp. Assuming an average hair growth of 1 cm/month (Wennig, 2000), this represents hair grown over a one-month period prior to sampling.

Samples were analyzed after each study wave in the laboratory of Prof Kirschbaum at the Technical University Dresden using a column-switching liquid chromatography atmospheric-pressure-chemical-ionization tandem mass spectrometry assay (LC–APCI–MS/MS). The protocol of this efficient, highly sensitive and reliable method for the quantification of steroid hormones in human hair is described elsewhere (Gao et al., 2013; Stalder et al., 2012). For cortisol, the intra- and inter-assay coefficients of variation (CVs) were found to range between 3.7 % and 8.8 % (Gao et al., 2013). All samples were analyzed ($n = 613$, mean hair mass = 6.6 mg).

2.3.2.2. C-reactive protein (CRP). All participants provided capillary blood samples for analysis of high-sensitivity C-reactive protein (hs-CRP). We used the well-established minimally invasive dried blood spot method in which drops of whole blood from a finger prick are collected on filter papers (McDade et al., 2007). A trained member of the study team pricked the participant's fingertip with a disposable lancet under sterile conditions, and after wiping away the first drop with gauze, applied at least two blood spots of sufficient size on a filter paper. The paper was then dried at room temperature for at least 8hr before being stored with a desiccant in a sealable multi-barrier pouch at −26 °C. Hs-CRP was analyzed using a "Human C-Reactive Protein/CRP Quantikine ELISA Kit" (IBL International) in the laboratory of the Chair of Health Psychology, Friedrich-Alexander University Erlangen-Nürnberg (Becker et al., 2022b for more details). The intra-assay CVs were 4.18 % (T1), 4.28 % (T2), and 4.06 % (T3). According to established cut-offs, hs-CRP values below 1.0 mg/L indicate a low, from 1.0 to 3.0 mg/L an average and above 3.0 mg/L a high risk for the development of cardiovascular diseases (e.g., Pearson et al., 2003).

2.4. Statistical analyses

The investigation of our research questions was based on the follow-up data, that is, T2 and T3, only. At baseline (T1), the majority of participants (66.1 %) had not started their job and almost half (45.8 %) were off duty (≥3 weeks) in the previous four weeks (for more information see Kaltenegger et al., 2023). Therefore, a valid assessment of participants' work situation as well as stress-related biomarkers at T1 was limited. In light of the panel attrition between T2 and T3 (~20 %), missing value analysis was performed with IBM SPSS Statistics (Version 29). 9.68 % of the values were missing and Little's MCAR test showed that missing data were not missing completely at random ($\chi^2 = 1176.16$, $df = 1056$, $p = .006$). Therefore, we imputed data using two consecutive methods: For control variables, missing T3 values were replaced by the within person mean of the respective T1 and T2 values. For key study variables, multiple imputation was conducted by creating five imputation datasets and pooling them to replace missing values. After imputation of missing data, the final sample size was $n = 238$ for each wave.

First, descriptive analyses as well as Pearson correlations and ANCOVAs for associations between study variables were conducted in SPSS. Next, we performed structural equation modelling in Mplus (Version 8.9, Muthén and Muthén, 2017) consisting of two steps: First, a confirmatory factor analysis (CFA) was conducted to corroborate the factorial structure of the questionnaire measures (general work stress, technostress, burnout symptoms) at T2 and T3. To test for multicollinearity, we performed linear regressions and checked tolerance statistics (Field, 2009). Second, in order to test our research questions, we performed path analysis models based on the full panel design using maximum likelihood estimation with robust standard errors (MLR) to account for any skewness in the data (Yuan and Bentler, 2000).

Full panel designs, in which both predictor and outcome variables are assessed at all waves, allow for the testing of both *normal* or *stressor-to-strain*, that is, prospective effects of job characteristics on health, and *reversed* or *strain-to-stressor* effects, that is, prospective effects of health on the evaluation of job characteristics (Taris and Kompier, 2014). For research question 1, we performed a path analysis model (model I) on cross-lagged effects between the predictors (general work stress, technostress) and outcomes (burnout, HCC, CRP) including normal effects (i.e., predictors at T2 on outcomes at T3) as well as reversed effects (i.e., outcomes at T2 on predictors at T3). For research question 2 (model II), we ran the same model with additional cross-lagged associations among all outcome variables (i.e., outcomes at T2 on outcomes at T3). Both models also included cross-sectional (i.e., synchronous associations at T2/T3) and autoregressive (i.e., stability paths T2–T3) effects of all study variables as well as a predefined set of confounders. The self-report variables (general work stress, technostress, burnout symptoms) were adjusted for sex (T1), age (T1), profession (T1), shift work (T3), and full-time job (T3). The biomarkers (HCC, CRP) were additionally controlled for BMI (T1), physical activity (T3), smoking (T3), and contraceptive use (T3). Model fit was evaluated using comparative fit index (*CFI*), root mean squared error of approximation (*RMSEA*), and standardized root mean square residual (*SRMR*). The following cut-offs indicated adequate fit: $CFI > 0.90$, $RMSEA \leq 0.06$, $SRMR \leq 0.08$ (Hu and Bentler, 1999).

3. Results

3.1. Descriptives

In the final sample ($n = 238$), the majority of participants was female ($n = 182$, 76.5 %). Participants were mainly nurses ($n = 67$, 28.2 %), followed by physicians ($n = 53$, 22.3 %), research personnel ($n = 35$, 14.7 %), medical-technical personnel ($n = 34$, 14.3 %), administrative staff ($n = 14$, 5.9 %), and other ($n = 32$, 13.4 %, such as midwives, therapists etc.). The mean age was ($M \pm SD$) 28.5 ± 8.4 and the mean BMI was 23.47 ± 4.52.

Main variable means at T2 and T3 are shown in Table 1. Regarding general work stress, job demands significantly increased over time. For technostress, work interruptions and information overload were significantly higher at follow-up. As for the outcome variables, burnout symptoms and HCC increased significantly, whereas CRP did not change significantly. Pearson correlations between work stressors, burnout symptoms, HCC, and CRP at T2 and T3 are depicted in Table 1A (Appendix).

3.2. Factorial structure of questionnaire measures

The CFA for both T2 (Fig. 1A, Appendix) and T3 (Fig. 2A, Appendix) showed that the scales work interruptions (T2: $\lambda = 0.77$, T3: $\lambda = 0.82$), multitasking (T2: $\lambda = 0.76$, T3: $\lambda = 0.79$), and information overload (T2: $\lambda = 0.59$, T3: $\lambda = 0.70$) loaded significantly and positively on a single latent factor "technostress". Furthermore, job demands (T2: $\lambda = 0.76$,

Table 1
Means, standard deviations (SDs), and paired t-tests of main variables at T2 and T3.

	T2 Mean (SD)	T3 Mean (SD)	Cohen's *d*	*p*
Job demands [1]	2.91 (0.99)	3.03 (0.97)	0.16	0.013
Job control [1]	3.03 (0.95)	3.00 (0.88)	0.04	0.580
General work stress (demand-control ratio) [2]	1.10 (0.62)	1.14 (0.63)	0.08	0.237
Technostress: subscale work interruptions [1]	2.71 (0.93)	2.84 (0.81)	0.22	<0.001
Technostress: subscale multitasking [1]	3.22 (1.17)	3.21 (1.12)	0.01	0.896
Technostress: subscale information overload [1]	2.30 (0.89)	2.43 (1.03)	0.16	0.016
Technostress: composite score	2.74 (0.81)	2.83 (0.82)	0.17	0.008
Burnout symptoms: exhaustion [3]	2.54 (0.84)	2.69 (0.90)	0.24	<0.001
Burnout symptoms: mental distance [3]	1.80 (0.77)	1.97 (0.81)	0.24	<0.001
Burnout symptoms: total	2.17 (0.69)	2.33 (0.76)	0.29	<0.001
Hair cortisol concentration (HCC, pg/mg)	4.79 (4.58)	9.56 (7.98) [+]	0.67	<0.001
C-reactive Protein (CRP, mg/L)	1.15 (1.51)	1.21 (1.37)	0.05	0.483

Note. $N = 238$; [+] $n = 237$.
[1] Scale range: 1 = not at all – 5 = to a very great extent.
[2] Range: 0.2 – 5.0.
[3] Scale range: 1 = never – 5 = always.

T3: λ = 0.64) loaded significantly positively and job control (T2: λ = −0.18, T3: λ = −0.17) negatively on the factor "general work stress". The BAT subscales exhaustion (T2: λ = 0.88, T3: λ = 0.89) and mental distance (T2: λ = 0.56, T3: λ = 0.63) were significant indicators of the factor "burnout". Model fit was excellent at both time points, *CFI* = 0.97 (T2)/0.98 (T3), *RMSEA* = 0.06 (T2&T3), *SRMR* = 0.04 (T2&T3). Therefore, composite scores (i.e., means for technostress and burnout; JDC ratio) at T2 and T3, respectively, were used. Tolerance statistics in four linear regressions with technostress, general work stress (i.e., JDC ratio), and burnout as predictors and HCC and CRP as outcomes at T2 and T3, respectively, were all > 0.2, indicating the variables satisfied the assumption of non-multicollinearity.

3.3. Prospective associations of technostress, general work stress, burnout symptoms, hair cortisol, and inflammation

We first tested the path analysis model for research question 1 (model I), that is, cross-lagged associations between predictors (technostress, general work stress) and outcomes (burnout, HCC, CRP) controlled for covariates (sex, age, profession, shift work, full-time job, BMI, physical activity, smoking, and contraceptive use). Results showed that technostress at T2 was significantly negatively associated with HCC at T3 (standardized coefficient β = −0.15, p =.003). In contrast, technostress at T2 was not significantly associated with burnout (β = 0.08, p =.133) and CRP at T3 (β = 0.04, p =.584). General work stress at T2 was not significantly associated with any of the outcomes at T3, that is, burnout (β = 0.01, p =.788), HCC (β = 0.06, p =.328), and CRP (β = −0.02, p =.824). Concerning reversed effects, there were no significant lagged associations with technostress or general work stress at T3: burnout (β = 0.07, p =.133; β = 0.02, p =.721), HCC (β = 0.02, p =.676; β = 0.03, p =.370) and/or CRP (β = 0.03, p =.373; β = 0.01, p =.853).

We then tested the adjusted path analysis model for research question 2 (model II), which additionally included cross-lagged associations between outcome variables (burnout, HCC, and CRP). The results of model II are presented in Fig. 1. Consistent with the results of model I, there was a significant negative effect of technostress at T2 on HCC at T3 (β = −0.16, p =.003), but no significant associations with the other outcomes. Again, general work stress at T2 was not significantly associated with any of the outcomes at T3, and there were no significant reversed effects. Concerning associations between outcomes, there was a positive cross-lagged effect of CRP at T2 on HCC at T3 (β = 0.28, p =.001). At the same time, there was a small negative effect of HCC at T2 on CRP at T3 (β = −0.10, p ≤.001). For burnout, there were no significant associations with HCC or CRP.

3.4. Additional analyses

To check for the robustness of the results, we ran the same two models including further relevant confounders for the biomarkers. First, HCC was additionally controlled for hair-related characteristics, that is, hair dyeing, hair treatment, washing frequency. The results were similar: For research question 1, there was still a significant negative effect of technostress at T2 on HCC at T3 (β = −0.17, p =.002). In model II, this effect remained significant as well (β = −0.17, p =.003), and there was still a positive effect of CRP at T2 on HCC at T3 (β = 0.24, p =.019) and a negative effect of HCC at T2 on CRP at T3 (β = −0.09, p =.002). Next, both HCC and CRP were additionally adjusted for season and hormone medication use not for contraception (n = 13, e.g., use of asthma inhalers containing corticosteroids). Again, the results were similar with a negative effect of technostress at T2 on HCC at T3 (Model I: β = −0.16, p =.003; Model II: β = −0.16, p =.005), a positive effect of CRP at T2 on HCC at T3 (β = 0.27, p =.005), and a negative effect of HCC at T2 on CRP at T3 (β = −0.08, p =.011). No other cross-lagged associations between main variables were significant. Fit indices for the final full model were *CFI* = 0.82, *RMSEA* = 0.07, *SRMR* = 0.08.

In addition, to further contextualize the associations between the key variables and the covariates, we conducted partial correlations and ANCOVAs using the adjustments applied in the path analysis models (Table 2). For age, there were significant negative correlations with general work stress and HCC. Shift workers reported higher general work stress. Profession had significant effects on technostress and general work stress with physicians reporting higher strain. BMI was positively correlated with HCC as well as CRP, and physical activity only with HCC. Smoking was negatively correlated with HCC. Contraceptive use was positively correlated with both biomarkers. Regarding season, there were significant effects for HCC with higher levels in summer–autumn and for CRP with higher levels in autumn than in winter (see Table 2).

4. Discussion

4.1. Findings and contributions to the literature

To the best of our knowledge, for the first time, the biological effects of work-related technostress in terms of HPA-axis function (i.e., HCC) and chronic low-grade inflammation (i.e., CRP) were investigated in a prospective study within a naturalistic occupational setting. Results showed that technostress was consistently negatively associated with HCC (research question 1) and that CRP was positively associated with HCC, while HCC was negatively associated with CRP (research question 2) over a time lag of 6 months. Given the lack of research – especially prospective – on work stress including technostress, HCC, and low-grade inflammation, our study contributes to the current evidence base in several ways.

First, in contrast to previous studies that often rely on subjective evaluations, we investigated physiological effects of technostress by measuring two key biological systems through which chronic stressors "get under the skin" and lead to disease, that is, the HPA-axis and the inflammatory system. The small literature that has assessed the association between technostress and biological stress responses have predominantly focused on acute stress responses (Becker et al., 2022a;

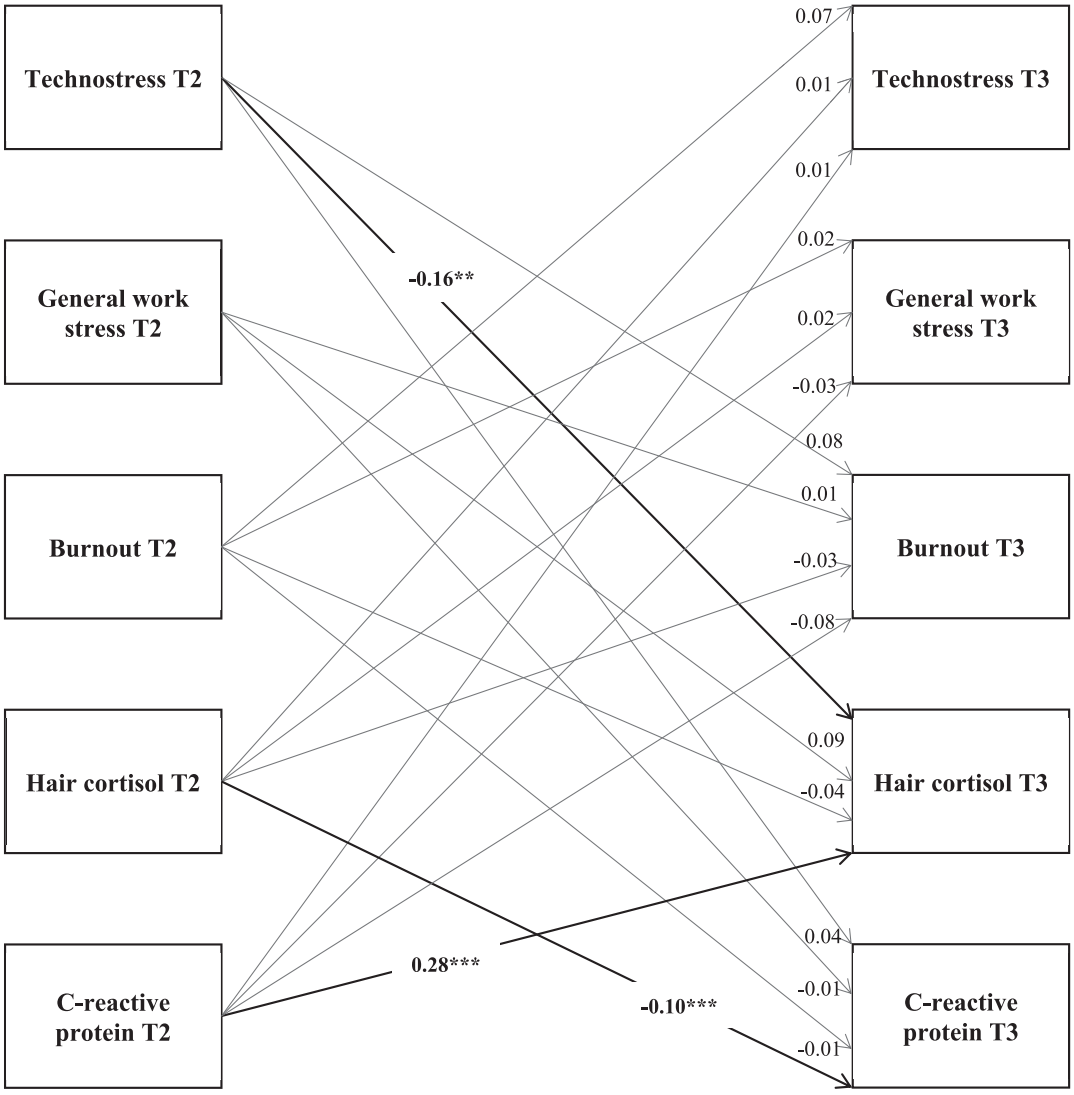

Fig. 1. Path model showing cross-lagged associations between technostress, general work stress (job demand-control ratio), burnout symptoms, hair cortisol concentration, and C-reactive protein at T2 and T3. *Note*. Standardized estimates. Adjusted for age, sex, profession, shift work, full-time job, and hair cortisol and C-reactive protein additionally for BMI, physical activity, smoking, use of contraceptives; cross-sectional and autoregressive associations are not shown; bold arrows indicate significant associations; ** $p \leq 0.01$, *** $p \leq 0.001$.

Riedl, 2012). In the present study, technostress (as measured by work interruptions, multitasking requirements and information overload due to digital technologies) was associated with reduced HCC, indicating a specific effect of technostress in terms of a longer-term alteration of HPA-axis activity beyond the influences of general work stress (i.e., JDC ratio). Consistent with our previous studies (Becker et al., 2023; Kaltenegger et al., 2023), we did not identify effects of technostress on the inflammatory system. However, these two studies were not prospective. Furthermore, general work stress was not significantly related to either HCC, or CRP, which adds to the limited and mixed evidence base on prospective associations of work stressors with HCC and low-grade inflammation (Kaltenegger et al., 2021; Schaafsma et al., 2021). Notably however, in model II, there was a weak positive, yet non-significant, association of general work stress with HCC. This aligns with a recent study in medical students showing a positive association of demands with HCC (Heming et al., 2023).

Second, given the paucity of longitudinal studies on technostress and mental health (Berg-Beckhoff et al., 2017; Dragano and Lunau, 2020), we contribute empirical insights into prospective associations with burnout as a key psychological outcome in chronic stress experience. Apart from a weak, non-significant association, we did not find prospective associations between technostress and burnout symptoms. This is not in line with findings from cross-sectional studies, which identified positive associations between constructs (e.g., Kaltenegger et al., 2023; Kasemy et al., 2022). Moreover, to provide a more comprehensive understanding of the pathways from burnout to health problems, we analyzed associations of burnout with the two biomarkers, revealing no significant prospective associations. Research on burnout and HCC is scarce with initial findings suggesting a non-linear relationship between accumulated burnout symptomatology and elevated HCC (Penz et al., 2018; Wendsche et al., 2020). Given that the burnout symptom levels in our sample were average and below clinical cut-offs (Schaufeli et al., 2023; Schaufeli et al., 2019), the null result seems plausible.

Third, our cohort study in a real work context complements and extends previous laboratory experiments providing external validity. The study was carried out in a high-risk environment for work-related stress in general, such as high work load or emotional stressors related to patient care, and technostress in particular due to health information technology use (Dawe et al., 2016; Melnick et al., 2020). Our results showed that technostress was rated as moderate across the sample with highest ratings in physicians, indicating that the assessed

Table 2
Associations of technostress, general work stress (job demand-control ratio), burnout symptoms, hair cortisol concentration (HCC), and C-reactive protein (CRP) with control variables (partial correlations and ANCOVAs).

Partial correlations (*r*; *p*)	Technostress T3	General work stress T3	Burnout T3	HCC T3	CRP T3
Sex T1 (male, female)	−0.01; 0.848	0.05; 0.421	0.11; 0.104	0.12; 0.102	0.09; 0.178
Age T1	−0.01; 0.912	−0.18; **0.007**	−0.11; 0.095	−0.17; **0.020**	−0.07; 0.308
Shift work T3 (no, yes)	0.06; 0.358	0.19; **0.004**	0.04; 0.511	−0.09; 0.225	0.00; 0.962
Full-time T3 (no, yes)	0.12; 0.075	0.06; 0.336	0.10; 0.117	−0.06; 0.444	0.09; 0.190
BMI T1	–	–	–	0.29; **<0.001**	0.36; **<0.001**
Physical activity T3 [1]	–	–	–	0.21; **0.004**	−0.03; 0.701
Smoking T3 [2]	–	–	–	−0.18; **0.011**	−0.07; 0.289
Contraceptive use T3 (no, yes)	–	–	–	0.15; **0.038**	0.27; **<0.001**
Hormone medication T3 (no, yes)	–	–	–	−0.13; 0.077	−0.03; 0.665
Hair dyeing T3 (no, yes)	–	–	–	0.10; 0.159	–
Hair treatment T3 (no, yes)	–	–	–	−0.01; 0.916	–
Hair washing frequency per week T3	–	–	–	−0.05; 0.487	–
ANCOVAs (*F* (*df*); *p*)					
Profession	*F*(5) = 6.23; **<0.001** [3]	*F*(5) = 3.05; **0.011** [4]	*F*(5) = 0.30; 0.911	*F*(5) = 0.26; 0.934	*F*(5) = 0.23; 0.951
Season, for HCC (T2 & T3)	–	–	–	*F*(7) = 17.49; **<0.001** [5]	–
Season, for CRP (T2 & T3)	–	–	–	–	*F*(3) = 4.95; 0.002 [6]

Note. Text in bold if significant at $p < 0.05$.
[1] Scale range: 1 = not at all – 5 = very much.
[2] Scale range: 1 = never smoked – 5 = yes, every day.
[3] Post-hoc tests with Bonferroni correction: Technostress at T3 was significantly higher in physicians than in nurses, medical-technical personnel, research staff, and other professions.
[4] Quade non-parametric ANCOVA with Bonferroni correction: general work stress at T3 was significantly higher in physicians than in nurses.
[5] Quade non-parametric ANCOVA with Bonferroni correction: HCC in summer, summer/autumn, and autumn was significantly higher than in autumn/winter, winter, winter/spring and spring, and HCC in spring/summer was significantly higher than in winter/spring.
[6] Quade non-parametric ANCOVA with Bonferroni correction: CRP in autumn was significantly higher than in winter.

technostressors – especially multitasking with the highest means – played a relevant role at participants' workplaces. The identification of at-risk persons and specific adverse working conditions is a crucial starting point for the prevention of stress-related diseases in healthcare professionals.

4.2. Post-hoc explanations for observed findings

As our main finding of an inverse association of technostress with HCC contradicts the traditional view of HPA-axis activity increases with stress, we suggest the following possible post-hoc explanations. On the one hand, this finding could be explained by hypocortisolism as a consequence to chronic stress. In their large-scale meta-analysis Miller et al. (2007) found that timing plays a critical role with elevated HPA-axis activity at stressor onset but a reduction over time, hence providing an explanation for the formerly conflicting findings of both hyper- and hypocortisolism in response to stress. Concerning work stress in particular, this two-stage notion of HPA-axis activation was also supported by a previous study, which found that increased effort-reward-imbalance was prospectively associated with decreased HCC indicating a blunted cortisol response (Penz et al., 2019). Regarding our results, one could hypothesize that although HCC increased over time, participants who experienced higher amounts of technostress had a lower HCC response at the next time point, which suggests dampened HPA-axis activity due to long-term work stress. Between baseline (T1) and T2 during the phase of organizational socialization in the new job, participants might have perceived high stress levels due to intensive learning and adaptation requirements. In addition, we can only speculate that before commencing their new employment, some participants might have been exposed to chronic stressors, such as high job demands in former jobs, demanding medical education, unemployment, or also other chronic stressors in their private lives. However, burnout levels in our sample, although increasing over time, were rather low, which might be due to the early phase of employment in most of the participants. In contrast to burnout and HCC, CRP did not change significantly over time, and this could possibly be explained by high starting values facilitating a ceiling effect. Yet, baseline CRP levels in our sample were comparable to levels in other samples including healthy (and young) adults and analyzed with the same method (Becker et al., 2023; Becker et al., 2022b).

On the other hand, another plausible explanation could be that participants who reported high levels of technostress in fact showed less physiological stress as indicated by decreased HCC. According to the integrated specificity model, the physiological stress response is not uniform, but shaped by the nature of the stressor and the individual cognitive appraisal of it (Kemeny, 2003). Drawing upon the Transactional Model of Stress (Lazarus and Folkman, 1984) physiological responses are substantially influenced by the appraisal of the stressor, that is, whether it poses a challenge or a threat, its perceived controllability and whether it threatens social status or self-esteem (Kemeny, 2003). In our study, participants might have evaluated the technostressors as a challenge with high chances of mastery and sufficient coping capabilities to meet the work demands. Technostressors that are appraised as challenge stressors, that is, as beneficial for accomplishing work tasks, were shown to be associated with positive emotions, which in turn was related to high job satisfaction in nurses (Califf and Sarker, 2020). Furthermore, even though technostressors, such as work interruptions, may be perceived as uncontrollable, they might also be regarded as a legitimate, integral part of the job in healthcare (Semmer et al., 2019) and therefore, as predictable or even "self-chosen". Finally, our operationalization of technostressors did not directly include a social-evaluative component, what together with uncontrollability is suggested to elicit a strong HPA-axis activation (Dickerson and Kemeny, 2004). Taken together, the specific nature of technostress and its cognitive appraisal by the employees might have led to a more favorable physiological response.

Eventually, we identified reciprocal associations between CRP and HCC. The finding of a positive effect of CRP on HCC supports the notion of glucocorticoid resistance, meaning that inflammation leads to an impairment of the negative feedback loop of the HPA-axis, which in turn leads to *hypercortisolism* (Pariante, 2017). At the same time, the finding of a negative effect of HCC on CRP confirms the established understanding of an anti-inflammatory effect of cortisol (see Sorrells and Sapolsky, 2007).

4.3. Limitations

Our findings need to be reflected in the light of several important limitations. First, regarding internal validity, it remains an open question whether the technostress scales measured stress *induced* by ICTs or rather work stress per se simply *mediated* by ICTs, that is, ICTs as a primary stressor versus medium transmitting common work stressors (Benlian, 2020). However, scale reliability was good, and factorial validity was confirmed. Moreover, we assessed burnout symptoms with a well-established, yet for the sake of practicability and efficiency, an abbreviated measure. We acknowledge that hence, the full burnout symptomatology was not captured. We used a parsimonious measure consisting of the two core dimensions of burnout, inability (i.e., exhaustion) and unwillingness (i.e., mental distance) to spend work-related effort, as suggested in previous literature (Schaufeli and Taris, 2005). Only two items per subscale were used, yet even single-item measures for burnout in healthcare providers have proven useful (Rohland et al., 2004; West et al., 2009). Although we controlled for a broad set of covariates, we cannot preclude confounding influences on stress perceptions and physiology by external factors, e.g., due to the Covid-19 pandemic or geopolitical events. Furthermore, because of threats to validity at T1, we had to constrain our design to two waves with a time lag of 6 months. It remains thus unclear, if the length of this interval was appropriate to capture the "true" effect, and the inclusion of a third (or even more) measurement time point(s) would have provided deeper insights into trajectories or potential mediating effects (Ployhart and Vandenberg, 2010; Taris and Kompier, 2014). Nonetheless, the application of the full panel design allowed us to test for normal, reversed, and reciprocal causality at the same time to unveil potential interactions of work characteristics, psychological states, and stress physiology (Taris and Kompier, 2014).

Concerning external validity, our data stemmed from young hospital employees, and that limits the generalizability of our findings to other age groups and professions. Moreover, although representative for healthcare, our sample was predominately female. Hence, our findings ought to be replicated among more experienced workers in different professional fields with a higher proportion of males.

4.4. Implications for research and practice

Given the infancy of research on health-related effects of technostress, our exploratory study provides important implications for future research. First, it advocates the viability of biomarker measurements in the quest for physiological correlates of technostress. For the rather novel approach of HCC analysis, our study provides further evidence for associations with covariates, which should be considered in future research. Compared to the meta-analysis by Stalder et al. (2017), we also identified significant associations with relevant covariates like BMI, age, and contraceptive use (the latter two however in different directions), but not with others (such as sex, hair washing frequency, and hair treatment), although comparability with our sample and method was limited. Moreover, our results suggested seasonal variation of HCC with higher concentrations in the summer and autumn than winter and spring months. This is in line with some of the few existing studies (Braig et al., 2015; Staufenbiel et al., 2015), but not with others (Abell et al., 2016). Regarding low-grade inflammation, CRP is an important indicator for the risk of cardiovascular diseases, which was in the average range in our sample. Yet, future studies should also consider further biomarkers, such as cytokines or cytokine imbalance for a more comprehensive understanding of inflammation and interactions with cortisol (Kaltenegger et al., 2020 for a list of inflammatory markers, Sorrells and Sapolsky, 2007). Building on our preliminary findings, more prospective studies with advanced, that is, full panel, designs and longer follow-ups are needed to investigate chronic psychophysiological effects of technostress and long-term health consequences.

If supported by future research, our findings have important implications for occupational health and safety in digitalized work environments. Chronic alterations of the HPA-axis activity are involved in a broad range of medical conditions, such as diabetes or obesity, and psychiatric conditions, such as depression or psychosomatic disorders (Chrousos, 2009; Miller et al., 2007). Technostress at work might therefore pose a health risk, which warrants the development of targeted prevention and intervention measures. At the same time, technology can be a useful tool for stress management at work, as was shown for a smartphone-based mindfulness meditation training intervention which reduced pro-inflammatory gene expression in customer service workers (Dutcher et al., 2022).

4.5. Conclusions

In conclusion, for the first time, this cohort study explored associations of technostress, general work stress, burnout symptoms, HCC, and chronic low-grade inflammation in a prospective repeated measurement design. The results provide preliminary indications for HCC alterations in hospital employees due to technostress. Moreover, the study yields insights into the complex interplay of the HPA-axis and inflammation. More prospective studies on the biological mechanisms linking chronic stress with disease are essential to improve our understanding of the potential health risks for workers in digitalized work settings.

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CRediT authorship contribution statement

Helena C. Kaltenegger: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mathew D. Marques:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Linda Becker:** Writing – review & editing, Methodology, Conceptualization. **Nicolas Rohleder:** Writing – review & editing, Methodology, Conceptualization. **Dennis Nowak:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Bradley J. Wright:** Writing – review & editing, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Matthias Weigl:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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

After internal approval of the data security committee of LMU university hospital, the study's minimal and anonymized underlying data set will be available from the corresponding author [HCK] upon

reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.01.222.

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3. Discussion

3.1 Main Findings and Contributions of the Dissertation

Chronic low-grade inflammation and the HPA axis have been identified as key pathways that link chronic stress to disease development (Miller et al., 2007; Rohleder, 2019). However, research on work stress, particularly technostress, and associations with alterations in these stress systems is scarce. This dissertation systematically investigated the chronic effects of working conditions and technostress on physiological stress responses and psychological health outcomes within naturalistic occupational contexts. Through an innovative method that included biomarker measurements, prospective study designs, and a combination of evidence synthesis and original research, this compilation of five articles advances the knowledge on health risks for employees in (digitalized) work environments:

To the best of the author's knowledge, Paper I and Paper II provided the first systematic review and meta-analysis on prospective associations between working conditions and chronic low-grade inflammation among employees. They showed that the existent study base was limited and heterogeneous, and there was a lack of studies on technostress and low-grade inflammation. However, for workplace interventions, the meta-analysis demonstrated that physical activity interventions (such as yoga or cycling to work) significantly reduced inflammation (i.e., CRP levels).

To address the identified research gaps, two original studies were conducted in real work settings among high-risk populations (i.e., healthcare professionals): Original study 1 investigated psychosocial working conditions based on the job demand–control–support model (Johnson & Hall, 1988; Karasek, 1979) and two biomarkers of chronic low-grade inflammation (i.e., CRP and leukocyte count) in geriatric care professionals (Paper III). The results revealed an association between high job autonomy and increased

CRP levels, which challenged the traditional conception of autonomy as a resource (Karasek, 1979), but adds to the emerging literature suggesting dysregulated physiology in specific conditions with increased autonomy (e.g., O'Donnell et al., 2015; Weigl et al., 2019).

In original study 2, the effects of technostress on chronic low-grade inflammation (i.e., hs-CRP) and long-term HPA axis activity (hair cortisol) were investigated for the first time in a prospective cohort study among hospital employees (original study 2a: Paper IV & original study 2b: Paper V). The results showed no significant associations of general work stressors or technostressors with hs-CRP, neither in the cross-sectional analysis of the baseline data (Paper IV) nor in the prospective analysis based on follow-up data (Paper V). Moreover, given the limited research on technostress at work and mental health (Dragano & Lunau, 2020), associations with burnout symptoms were assessed in original study 2. In the cross-sectional analysis, various technostressors were significantly associated with burnout symptoms (Paper IV). More specifically, the technostressor techno- and information overload, i.e., increased work load and perceived information flood due to ICTs (Piecha & Hacker, 2020; Tarafdar et al., 2007), predicted exhaustion and mental distance even after statistically adjusting for general work overload, suggesting a distinct effect of this technostressor on employees' psychological health (Paper IV). However, in the prospective analysis within original study 2b, technostress as a composite measure of work interruptions, multitasking, and information overload was not significantly associated with burnout symptoms (Paper V). Regarding hair cortisol, adjusted path analysis models showed that technostress, but not general work stress, was consistently negatively associated with hair cortisol levels over time (Paper V). This negative association could possibly be explained on the one hand by *hypocortisolism* due to chronic stress (Heim et al., 2000), but on the other hand by a more favorable stress response due to potential positive appraisals of technostress.

Furthermore, there were reciprocal prospective effects of hs-CRP on hair cortisol concentration and vice versa, but no associations of the biomarkers with burnout symptoms were observed (Paper V).

Drawing upon an advanced method including prospective designs and multi-source data from real-world work settings, this dissertation significantly contributes to the understanding of the nowadays highly relevant phenomenon of technostress and its physiological as well as psychological health outcomes in high-risk employees. Taken together, with reference to the overall research question of the dissertation, the results suggest that technostressors at work—beyond general work stressors—are associated with physiological effects (i.e., HPA axis activity) and specific technostressors potentially with psychological health sequelae (i.e., burnout symptoms) in healthcare professionals.

3.2 Limitations and Strengths

The findings of this dissertation should be reflected in the light of some important limitations. First, regarding study designs, Paper III and Paper IV were based on cross-sectional analyses; therefore, their results do not allow for inferences on causality. However, Paper II and Paper V relied on prospective designs, which offer significant advantages over cross-sectional designs in investigating causal relationships in occupational health research (Taris & Kompier, 2014). In particular, a full panel design, such as that used in Paper V, enables testing of both *stressor-to-strain* (i.e., lagged effects of working conditions, including technostress, on physiological and psychological variables) and *strain-to-stressor* effects (i.e., lagged effects of physiological and psychological variables on the appraisal of working conditions), providing insights into normal, reversed, or reciprocal causality (Taris & Kompier, 2014).

Second, concerning the measurements of study variables, one important limitation pertains to the selection and operationalization of the predictors (i.e., general work stressors and technostressors). In occupational health research, a variety of models have been established on different job characteristics and hypothesized associations with employee well-being and health as well as work-related outcomes. In Paper I, for the systematic review, a comprehensive criteria-based classification of working conditions was developed (see Paper I, p. 6). However, in the original studies, for reasons of efficiency and practicability, only a limited number of job demands (work overload) and job resources (control, social support) were assessed. In line with the differentiated job demands–resources model, distinct effects of *challenge* and *hindrance* demands, which are suggested to be differently associated with employee outcomes (e.g., work engagement and exhaustion), should also be considered (Crawford et al., 2010; van den Broeck et al., 2010). Accordingly, in Paper IV, *challenge technostressors*, i.e., technology characteristics that are appraised by the user as helpful for task accomplishment, were distinguished from *hindrance technostressors*, which are appraised as disturbing for work-related achievement (Califf & Sarker, 2020; Cavanaugh et al., 2000; Tarafdar et al., 2019). However, more studies are needed, ideally with longitudinal designs, to investigate a broad range of job characteristics and their potential additive as well as interactive (i.e., buffering or boosting) effects on physiological stress reactions and psychological health outcomes (Schneider et al., 2017). Furthermore, it remains a challenge for future research to clearly separate general work stress from technostress. It has been discussed that technology could either be a primary stressor (e.g., unreliability) or simply a medium through which established work stressors (e.g., job demands) are transmitted (Benlian, 2020; Dragano & Lunau, 2020). This issue was addressed in the dissertation by thoroughly examining the reliability and factorial validity of the technostressor scales, statistically controlling for general work stressors, and checking for potential interaction

effects (Papers IV & V). Moreover, for the measurement of chronic low-grade inflammation, this work focused on CRP, because it is regarded as a sensitive and reliable marker of inflammation and frequently used in work stress research (Hänsel et al., 2010; Pepys & Hirschfield, 2003; Wright et al., 2020). However, as inflammation can be measured on different molecular biological levels (i.e., cells, plasma molecules, intracellular processes, see Paper I), future studies should include further inflammatory markers to test the robustness of the results. Regarding psychological health, only burnout symptoms were assessed with a well-established but shortened measure and hence, not the full symptomatology (Papers IV & V). Concerning potential confounding variables, although in the original studies (and partially in the systematic review) large sets of relevant covariates were included, further factors that could influence work stress experience cannot be ruled out, such as participants' personal characteristics (e.g., overcommitment, Eddy et al., 2016) or social circumstances (e.g., caregiving to a relative, Rohleder, 2019).

Third, regarding external validity, the generalizability of the findings is limited to the working population with a specific focus on healthcare professionals. Although representative of the healthcare sector, the samples in the original studies consisted predominantly of women, limiting the possibility of investigating potential sex differences. Moreover, in original study 2, due to the specific recruitment method (i.e., pre-employment medical examination) and strict eligibility criteria, the sample included mainly healthy and rather young participants with short professional tenures, potentially eliciting a floor effect concerning chronic stress experience (Papers IV & V). However, it is noteworthy that mean hs-CRP levels in this sample were > 1 mg/ L, indicating an average risk for cardiovascular diseases according to established cut-offs (Pearson et al., 2003) and that chronic low-grade inflammation played a role in this sample (Papers IV & V).

A particular strength of the dissertation is the implementation of *open science* practices for transparency and reproducibility throughout the entire research process. For instance, study protocols were developed and registered (Papers I, II, IV, & V), underlying (anonymized) datasets were made publicly available (Papers II & III), and results were published with open access (Papers I–V). Further strengths pertain to the method of original study 2, where a novel biomarker for chronic stress (i.e., hair cortisol) was measured and a large number of participants included thanks to intensive sampling.

3.3 Implications for Future Research

The following important avenues for future research can be derived from this dissertation: First, the findings provide support for the utility of biomarkers to investigate influences of working conditions in general and technostress in particular on employee health alongside self-report measures. In occupational stress research, self-report is often the means of choice and the technostress research is almost entirely based on this method. However, using self-report for both independent and dependent variables involves the problem of common method variance, which can lead to inflated or spurious results (Semmer et al., 2003). This calls for the inclusion of alternative methods, such as biomarkers, to objectively measure stress reactions. In contrast to self-report, physiological processes are less easily influenced by the respondent or the experimenters' expectations. Therefore, for a valid and reliable assessment of occupational stress, future research should combine various methods, such as subjective self-report with physiological data (Semmer et al., 2003).

Second, more prospective studies on working conditions, chronic low-grade inflammation, and hair cortisol are needed, ideally with full panel designs, to corroborate the results. For instance, in original study 2, more follow-up measurements and different

lengths of time lags should be established to increase chances of capturing effects and to investigate long-term health consequences (Taris & Kompier, 2014).

Third, as to the best of the author's knowledge, original study 2 was the first to assess associations of technostress with low-grade inflammation and hair cortisol concentration, further empirical evidence on technostress and biological mechanisms that link chronic stress to disease development is necessary. More specifically, additional technostressors should be considered, especially more recent developments such as artificial intelligence-based technologies (Dragano & Lunau, 2020). In addition to the negative effects of technostress, positive ramifications for employee health and well-being should be investigated further. For example, in Paper IV, the technology aspects appraised as beneficial for job tasks (i.e., challenge technostressors, see chapter 3.2), such as usefulness or technical support provision, were not related to low-grade inflammation or burnout symptoms. However, positive psychological responses to challenge technostressors have been reported in previous studies (e.g., Califf & Sarker, 2020). Finally, stress systems should not be assessed in isolation but rather in interaction with other stress axes. The results of the additional Papers VI and VIII showed that technostress was associated with acute activation of the sympathetic nervous system. With regard to long-term health, it would be insightful if technostress leads to chronic overactivation of the sympathetic nervous system, which can result in cardiovascular diseases such as hypertension (Becker, Kaltenegger, Nowak, Rohleder, & Weigl, 2023).

3.4 Implications for Occupational Health Practice

Within an overall view, this dissertation suggests that technostress might present a health risk and this has important implications for occupational health practice. Poor physical and mental health of the workforce is costly for affected individuals, employers,

and the whole society (Rugulies et al., 2023). At the same time, workplace conditions offer important leverage points to prevent harm, promote health and well-being, and support employees with potential health problems (Rugulies et al., 2023). Therefore, as an outlook, this dissertation raises the question of how both working conditions and workers can be healthy in the age of digitalization. One possibility is that more organization-directed/ structural interventions are needed to improve working conditions in addition to individual-directed/ behavioral interventions. For instance, the meta-analysis showed that physical exercise interventions at the workplace can effectively reduce chronic low-grade inflammation in employees (Paper II). However, in contrast to merely addressing employee strain (such as inflammation), primary preventive measures that target the source of strain by changing working conditions are suggested to be more effective (LaMontagne et al., 2007). Specifically for dealing with technostress, examples for measures on an organizational level could be establishing a culture of efficient digital communication or provision of technical support, and for individual level interventions the improvement of employee digital literacy (Stadin et al., 2020). However, there is a lack of systematic prevention and intervention studies on technostress at work, which should be addressed by future research (Rohwer et al., 2022). For occupational health management, technostressors should be taken into account in psychosocial risk assessments at work (Diebig et al., 2018). Finally, as an implication for clinical care, the patient's work situation and conditions should be considered in detail in clinical assessments by psychologists, psychiatrists, general practitioners, and other health professionals for a better understanding and management of work stress-related symptoms and diseases (Rugulies et al., 2023).

3.5 Conclusions

The megatrend of digitalization has profoundly transformed the world of work. Therefore, it is timely to advance our understanding of the physiological and psychological correlates of modern (digitalized) working environments. This work offers a novel perspective by investigating biomarkers of chronic stress using advanced study designs in real-world and high-risk work settings. The findings provide valuable insights into how working conditions and technostress could be related to key physiological pathways through which stress “gets under the skin” and affects the long-term health of employees.

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Appendix

A. List of Conference Contributions and Talks

Becker, L., Kaltenegger, H. C., Nowak, D., Weigl, M., & Rohleder, N. (2021, June 2–4). *Physiological stress in response to dual- and multitasking demands – A systematic review and meta-analysis* [Poster presentation]. Psychologie und Gehirn (PuG), online.

Becker, L., Kaltenegger, H. C., Nowak, D., Weigl, M., & Rohleder, N. (2021, September 28–30). *Physiological stress in response to dual- and multitasking demands – A systematic review and meta-analysis* [Conference presentation]. 15. Kongress der Fachgruppe Gesundheitspsychologie der DGPs, online.

Kaltenegger, H. C. (2021, March 17). *Association of working conditions including digital technology use and systemic inflammation among employees: A systematic review and meta-analysis* [Poster presentation]. Nachwuchssymposium der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), online.
Awarded with poster prize.

Kaltenegger, H. C. (2023, March 9). *Brave New Work? Effects of Work with Digital Technologies on Stress and Mental Health* [Talk]. Seminar at the Department of Psychology, Counselling and Therapy, La Trobe University, Melbourne, Australia.

Kaltenegger, H. C., Becker, L., Quartucci, C., Rohleder, N., Nowak, D., & Weigl, M. (2022, March 23–26). *Schöne neue Arbeit? Zusammenhänge von Techno-Stressoren mit chronischer unterschwelliger Inflammation und Burnout bei Beschäftigten.* [Conference presentation]. 62. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), online.

Kaltenegger, H. C., Becker, L., Quartucci, C., Rohleder, N., Nowak, D., & Weigl, M. (2023, March 15–18). *Schöne neue Arbeit? Zusammenhänge von Techno-Stressoren mit Burnout-Symptomen und Haar-Cortisol: Eine Längsschnitt-Studie bei Krankenhauspersonal* [Conference presentation]. 63. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), Jena, Germany [represented by Prof. Dr. Dennis Nowak].

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., Quartucci, C., & Weigl, M. (2022, September 8–10). *Associations between digital work stressors, burnout, and hair cortisol concentration: A prospective study* [Poster presentation]. 52nd Annual Meeting of the International Society of Psychoneuroendocrinology (ISPNE), Chicago, IL, United States. https://doi.org/10.1016/j.psyneuen.2023.106167
Awarded with poster prize.

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., Quartucci, C., & Weigl, M. (2023, May 24–27). *Associations between digital work stressors, burnout symptoms, and biological stress: A prospective study in hospital employees* [Conference presentation]. 21st Congress of European Association of Work and Organizational Psychology (EAWOP), Katowice, Poland.

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., & Weigl, M. (2021, March 17–20). *Association of working conditions including digital technology use and systemic inflammation among employees: A systematic review and meta-analysis* [Conference presentation]. 61. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), online.

Kaltenegger, H. C., Becker, L., Rohleder, N., Nowak, D., & Weigl, M. (2021, September 28–30). *Associations of working conditions and chronic low-grade inflammation among employees: A systematic review and meta-analysis* [Conference presentation]. 15. Kongress der Fachgruppe Gesundheitspsychologie der DGPs, online.

Kaltenegger, H. C., Marques, M. D., Becker, L., Rohleder, N., Nowak, D., Wright, B. J., & Weigl, M. (2023, August 30–September 1). *Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation* [Poster presentation]. 53rd Annual Meeting of the International Society of Psychoneuroendocrinology (ISPNE), London, England. https://doi.org/10.1016/j.psyneuen.2023.106866

Kaltenegger, H. C. & Weigl, M. (2021, September 21). *Schöne neue Arbeit? Belastungen, Stress und Bewältigung am Arbeitsplatz im Zeitalter der Digitalisierung* [Talk]. *#DigitalUmDrei* „Arbeitsplätze im Wandel“, online.

Quartucci, C., Kaltenegger, H. C., & Weigl, M. (2021, March 17–20). *Zusammenhänge zwischen psychosozialen Arbeitsbelastungen und subklinischen Entzündungsprozessen: Eine Multi-Methoden-Studie bei Pflegepersonal* [Conference presentation]. 61. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), online.

B. Scientific Posters

Table A1

Overview of Scientific Posters Presented at Conferences

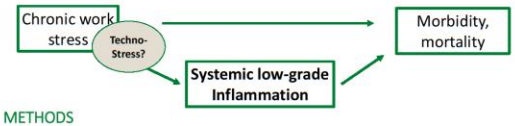
Title	Conference, year, location	Page
Association of working conditions including digital technology use and systemic inflammation among employees: A systematic review and meta-analysis	Nachwuchssymposium der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM), 2021, online	127
Associations between digital work stressors, burnout, and hair cortisol concentration: A prospective study	52nd Annual Meeting of the International Society of Psychoneuroendocrinology (ISPNE), 2022, Chicago, IL, United States	128
Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation	53rd Annual Meeting of the International Society of Psychoneuroendocrinology (ISPNE), 2023, London, England	129

LMU KLINIKUM

Institute and Clinic for Occupational, Social and Environmental Medicine
University Hospital, LMU Munich
Clinical Director Prof. Dr. Dennis Nowak

Associations of working conditions including digital technology use and systemic inflammation among employees:
A systematic review and meta-analysis

BACKGROUND



METHODS

Eligibility criteria:

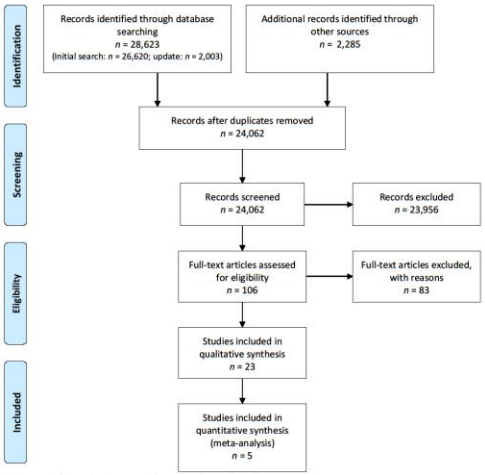
Participants: all types of adult workers

Exposures/**I**nterventions: all kinds of working conditions and workplace-related interventions

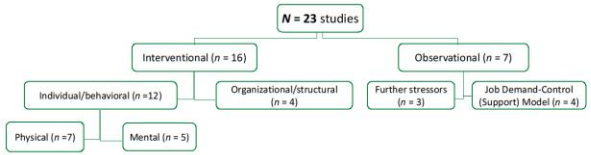
Comparators: not/ to a lesser extent exposed to a specific working condition/ intervention

Outcomes: biomarkers of systemic low-grade inflammation (blood, saliva)

Study design: prospective (interventional, observational)



PRISMA Flow diagram for study selection



Overview of included studies by design and exposure

Forrest plot of random effects meta-analysis on workplace physical interventions and CRP (N = 242; k = 5; d = -0.61, p < .001)

RESULTS

Workplace **physical** interventions & inflammation:

- Meta-analysis: significant reduction in CRP

Workplace **mental** interventions & inflammation:

- Indications for changes in intra-cellular inflammatory processes (e.g. gene expression)

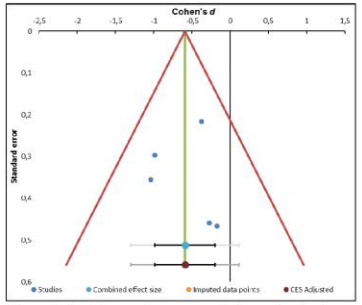
Organizational interventions & inflammation:

- Mixed results

Psychosocial working conditions & inflammation:

- Weak evidence, yet indications for protective effects (social support, control)

Scarcity of studies on work-related use of digital technologies and systemic inflammation!



Funnel plot for studies on workplace physical interventions and CRP

LIMITATION

Heterogeneous and limited study base

For Digit Health
Bayerisches Staatsministerium für Wissenschaft und Kunst

Helena C. Kaltenegger*, Linda Becker, Nicolas Rohleder, Dennis Nowak, Matthias Weigl

** Correspondence: Helena C. Kaltenegger, M.Sc., Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstr. 1, 80336 Munich, Germany; helena.kaltenegger@med.uni-muenchen.de*

LMU KLINIKUM
University Hospital, Ludwig-Maximilians-University Munich
Institute and Clinic for Occupational, Social and Environmental Medicine
Director: Prof. Dr. Dennis Nowak

For Digit Health
Bayerisches Staatsministerium für Wissenschaft und Kunst

Associations between digital work stressors, burnout, and hair cortisol concentration: A prospective study

Helena C. KALTENEGGER[1], Linda BECKER[2], Nicolas ROHLEDER[2], Dennis NOWAK[1], Caroline QUARTUCCI[1,3], Matthias WEIGL[1,4]

[1] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany.
[2] Chair of Health Psychology, Institute of Psychology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany
[3] Bavarian Health and Food Safety Authority, Institute for Occupational Health and Product Safety, Environmental Health, Munich, Germany
[4] Institute for Patient Safety, University Hospital Bonn, Bonn, Germany

Introduction

- Despite the growing research interest into the concept of *technostress* [1], biological effects of work with digital technologies are under-researched [2,3].
- Analysis of hair cortisol concentrations (HCC) is a relatively new method to measure long-term cumulative cortisol levels retrospectively [4].
- Prospective studies including repeated measurements of work stress and HCC are scarce.

Objective

To assess prospective associations of (digital) work stressors, burnout symptoms (hereinafter named burnout) and HCC.

Methods

Design: Prospective cohort study

Participants:

- *N*=94 (75 females, $M \pm SD_{age}$=29.7±8.45 years) new employees at LMU University Hospital
- Exclusion criteria:
  - **A priori**: acute symptoms of illness, permanent anti-inflammatory medication intake, recent intake of anti-coagulant drugs, pregnancy
  - **A posteriori**: incomplete HCC data, extreme HCC values (> 3 SD from mean)

Measures:

- Work overload, job control [5]
- Digital work stressors: work interruptions, multitasking [5–7]
- Burnout symptoms (exhaustion, mental distance) [8]
- Hair cortisol concentration (HCC) [9]

Statistical analyses:

- Calculation of change scores: Δ =T2 – T1
- Linear regression

Correspondence to: Helena C. Kaltenegger, M.Sc.
helena.kaltenegger@med.uni-muenchen.de

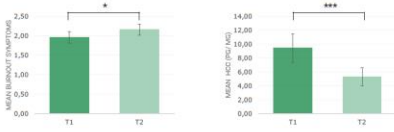
Interruptions by digital technologies at work are associated with cortisol in hair.

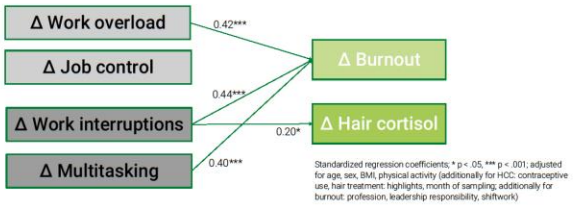
Abstract

Working conditions in the age of digitalization bear risks for chronic stress exposure and eventually development of burnout. Analysis of **hair cortisol concentration** (HCC) is increasingly used to capture cumulative cortisol secretion. We aimed at assessing associations of changes in (digital) work stressors, burnout, and HCC. *N*=94 hospital employees reported on job strain (work overload, job control), **digital work stressors** (work interruptions, multitasking), **burnout** symptoms (exhaustion, mental distance), relevant confounders and provided hair samples at baseline and 6 months later. We calculated change scores and multivariate linear regressions. Burnout increased significantly, while HCC decreased over time. **Work overload**, **work interruptions** and **multitasking** were associated with **burnout**. **Work interruptions** were further associated with **HCC**. This study extends the limited evidence base on **prospective** associations between workplace stress and HCC. To our knowledge, for the first time, a link of a digital work stressor with HCC was revealed.

Here you find the pre-registration of the study and the poster on osf.io

Results





Standardized regression coefficients; * p < .05, *** p < .001; adjusted for age, sex, BMI, physical activity (additionally for HCC: contraceptive use, hair treatment: highlights, month of sampling; additionally for burnout: profession, leadership responsibility, shiftwork)

Path diagram on associations between change scores (Δ) of predictors (work stressors) and outcomes (burnout, hair cortisol concentration)

- Increased work overload was associated with increased burnout. Job control was not associated with burnout. Increased interruptions and multitasking were associated with increased burnout, also after additionally controlling for changes in work overload (β=0.34, *p*=.001; β=0.30, *p*=.003).
- Increased interruptions were associated with increased HCC. Work overload, job control and multitasking were not associated with HCC.
- There were no linear relationships between burnout and HCC.

Associations of single time points: Work overload (T1) & burnout (T2): β=0.36, *p*=.001; interruptions (T1) & burnout (T2): β=0.13, *p*=.263; multitasking (T1) & burnout (T2): β=0.20, *p*=.061; interruptions (T1) & HCC (T2): β=-0.05, *p*=.640

Conclusions

- This study contributes to the limited research base on prospective associations of work stress and HCC.
- Work interruptions due to digital technologies were associated with HCC.
- Future research ought to replicate observed effects in other occupational samples and scrutinize potential non-linear associations of burnout and HCC.

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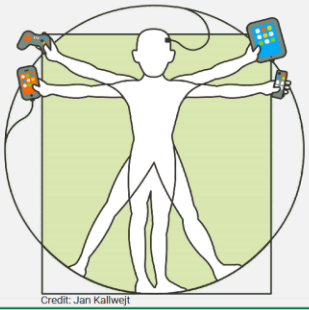
Director: Prof. Dr. Dennis Nowak

Prospective associations of technostress at work, burnout symptoms, hair cortisol, and chronic low-grade inflammation

Helena C. Kaltenegger[1], Mathew D. Marques[2], Linda Becker[3], Nicolas Rohleder[3], Dennis Nowak[1], Bradley J. Wright[2+] & Matthias Weigl[1,4+]

[1] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany
[2] School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia
[3] Institute of Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[4] Institute for Patient Safety, University Hospital Bonn, Bonn, Germany
[+] shared senior authorship

Does **technostress** get "under the skin"?



Credit: Jan Kallwejt

Working conditions in the age of digitalization harbour risks for **chronic stress** and **burnout**. However, real-world investigations into **biological effects** of **technostress** are sparse. This study prospectively assessed associations between technostress, general work stress, burnout symptoms, hair cortisol, and chronic low-grade inflammation.
Hospital employees participated in a **prospective cohort study** with two follow-ups six months apart. Participants answered questionnaires on **general job strain**, **technostressors,** and **burnout symptoms**. Moreover, they provided capillary blood samples for **C-reactive protein (CRP)** and hair strands for **hair cortisol concentration (HCC)** analysis. Structural equation modelling was performed.
Burnout symptoms and HCC increased over time, CRP did not. Adjusted path models showed that **technostress** was **negatively associated** with **HCC,** but not with burnout and CRP. General work stress in contrast, was not significantly associated with burnout, HCC or CRP. Furthermore, there were **reciprocal effects** of **CRP** and **HCC**.
This is the first study on prospective effects of technostress on employees' endocrine and inflammatory systems. Results suggest differential effects of technostress on the **hypothalamic-pituitary-adrenocortical axis** activity. Given its key role for long-term health, the findings have important implications for **occupational health and safety** in digitalized work environments.

INTRODUCTION

- *Technostress*[1]: "Stress experienced by end users of Information and Communication Technologies"[2]
- Lack of research on effects of technostress on stress physiology
- Two possible biological mechanisms in the link between stress and disease:
  - Hypothalamic pituitary-adrenocortical (HPA) axis with cortisol[3]
  - Inflammatory system [4]
- Healthcare professionals as at-risk population for work-related (techno-)stress

OBJECTIVE

To assess prospective associations of technostress, general work stress, burnout symptoms, hair cortisol, and chronic low-grade inflammation

METHODS

T1 Baseline — T2 Follow-up I (after 6 months) — T3 Follow-up II (after 12 months)

Design: prospective cohort study with full cross-lagged panel design

Participants:

- *N*=238 (182 females, $M_{age} \pm SD$ = 28.5 ± 8.4 years) new university hospital employees
- Exclusion criteria:
  - **A priori:** acute disease symptoms, permanent anti-inflammatory or anti-coagulant medication intake last 12h, pregnancy
  - **A posteriori:** dropout after T1, HCC levels > 3 *SD* from mean, CRP levels > 10 mg/L

Measures:

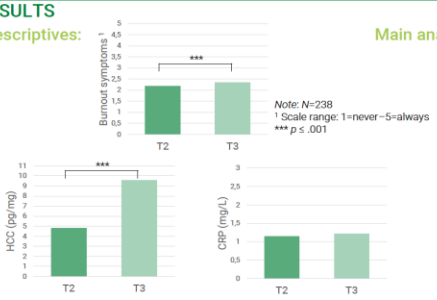
- General work stress: job demand/control ratio [5,6]
- Technostress: work interruptions, multitasking, information overload [5,7-9]
- Burnout symptoms: exhaustion, mental distance [10]
- HPA axis: Hair cortisol concentration (HCC) [11]
- Low-grade inflammation: C-reactive Protein (CRP) [12]

Statistical analyses:

- Structural equation modelling (Mplus) based on imputed data

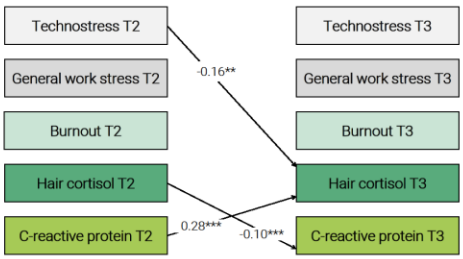
RESULTS

Descriptives:



Means of burnout symptoms, hair cortisol concentration (HCC), and C-reactive protein (CRP) at T2 and T3.

Main analysis:



Path model showing cross-lagged associations between technostress, general work stress, burnout symptoms, hair cortisol concentration, and C-reactive protein at T2 and T3.

Note. *N*=238. Standardized estimates. Adjusted for age, sex, profession, shift work, full-time job, and hair cortisol and C-reactive protein additionally for BMI, physical activity, smoking, use of contraceptives. Arrows show significant cross-lagged associations.
** $p \leq .01$, *** $p \leq .001$

Additional analyses:

Inclusion of further confounders:

- HCC: hair dyeing, hair treatment, hair washing frequency
- HCC and CRP: season of sampling, hormone medication use (not for contraception)

➢ Same results

DISCUSSION & CONCLUSIONS

- Key findings:
  - Technostress prospectively associated with reduced HCC ➡ specific effect of technostress in terms of longer-term alteration of HPA axis activity beyond general work stress
  - Positive association of CRP with HCC and negative association of HCC with CRP over time
- Posthoc explanations: stress-related hypocortisolism vs. lower stress response with technostress?
- Limitations: young, predominantly female sample of one professional field ➡ limited external validity
- Need for more prospective studies on biological pathways to improve understanding of health risks in digitalized work environments

Correspondence to: Helena C. Kaltenegger, M.Sc.
helena.kaltenegger@med.uni-muenchen.de

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