European Review for Medical and Pharmacological Sciences 2021; 25: 222-232

Shift or night shift work and dementia risk: a systematic review

V. LESO, A. CATURANO, I. VETRANI, I. IAVICOLI

Section of Occupational Medicine, Department of Public Health, University of Naples Federico II, Naples, Italy

Abstract. – OBJECTIVE: Dementia is a neurodegenerative disorder characterized by a progressive decline in multiple cognitive domains. Individual and/or environmental risk factors, i.e., aging, are involved in its pathogenesis. It is possible that shift and night works, affecting circadian rhythms, may contribute to the occurrence/progression of the disease. Therefore, aim of this review was to provide an overview on the possible association between shift or night work and cognitive decline.

MATERIALS AND METHODS: A systematic review of literature studies available in PubMed, Scopus, and ISI Web of Science databases, addressing the possible relationship between shift or night work and dementia was performed.

RESULTS: Not-homogeneous findings emerged from the revised studies. Some results supported a positive association between shift work and increased risk of dementia, although with a not unique evidence concerning the role of night work schedules and the consequent circadian misalignment in disease pathogenesis. Cardiometabolic disorders, underlying lifestyles, and additional occupational risk factors, including, psychosocial stress, may act as mediators in the shift work-dementia relationship, that may be overall affected by the individual genetic susceptibility too. Length of employment in shift works was also suggested to be responsible for cognitive damaging effects.

CONCLUSIONS: The limited number of available studies, the several and different work schedules analyzed, together with the possible co-exposure to other occupational risk factors prevent to draw conclusions on shift work-dementia relationship. Further research should confirm such association and the causal relation with early cognitive alterations in order to guide suitable occupational risk assessment, as well as to promote healthy lifestyle and occupational management strategies, with the ultimate goal of preventing cognitive decline of shift workers. This may overall support the active aging of the workforce while providing benefits for the public health system.

Key Words:

Dementia, Cognitive degeneration, Cognitive decline, Shift work, Night work, Circadian rhythm, Work schedule, Risk assessment, Risk management, Active aging.

Introduction

Dementia is a chronic neurodegenerative syndrome, characterized by a progressive decline in cognitive function, not accounted by underlying psychiatric conditions or mood disorders, and sufficiently sever to compromise social or occupational functioning[1]. Such decline can involve multiple mental domains, including learning, memory, language, complex attention, executive ability, perceptual-motor function and social cognition[2]. The most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) introduced the term "major neurocognitive disorder" to indicate, more specifically, all conditions of cognitive impairment defined as "dementia" until now. Its diagnosis requires the presence of substantial impairment in one or (usually) more cognitive domains, sufficient to interfere with independence in everyday activities[3,4]. Dementia comes in many forms, with the Alzheimer's and vascular subtypes being the most common[5].

The etiology of the disease is multifactorial[1,4]. Various genetic and/or environmental risk factors have been suggested as triggers of memory and learning loss symptoms that are the best known hallmarks of dementia. Among such risk factors, the strongest association was found for aging, with most dementia cases affecting individuals of 65 years and older[6,7]. Additionally, cardiovascular and metabolic comorbidities, including midlife hypertension, obesity and type 2 diabe-

Corresponding Author: Veruscka Leso, MD, Ph.D; e-mail: veruscka.leso@unina.it

tes, unhealthy lifestyles, i.e., smoking, alcohol or caffeine consumption, physical inactivity and social isolation and irregularities in the sleep-wake rhythm have been reported as possible contributing factors[8,9].

In this perspective, shift work, defined by the International Labour Organization as "a method of organization of working time in which workers succeed one another at the workplace"[10], and night work, intended by the European Union as "working at least 3 h of the daily shift or a certain proportion of the yearly working time in a period of 7 h defined by national law and including the time from midnight to 05:00"[11,12], may have an influencing role in the dementia's pathogenesis. Shift works, and particularly night works, in fact, may act as modifiable risk factors chronically affecting circadian rhythms and cardiovascular functionality in exposed workers, thus influencing the development and the evolution of the neurodegeneration process[13-18].

In this scenario, the aim of the present review was to comprehensively assess the possible relationship between shift or night shift work and the occurrence/progression of dementia, and to evaluate possible underlining pathogenetic mechanisms, including the interplay with personal risk factors, in cognitive decline manifestation. This may provide guidance to health care specialists, occupational physicians and employers to achieve a suitable clinical and occupational management of shift workers. This may include the adoption/implementation of primary, early, midlife, preventive and protective strategies to manage such modifiable occupational risk factors. This could provide workers efficient support to face occupational exposures and prevent neurocognitive degeneration during the working age and in the elderly. Overall, taking into account both the high global prevalence of shift works, including night works, and the strong and lifelong impact of the disease on the patients' quality of life and health care resources, an early management of the occupational and personal risk factors for dementia my provide benefits from a public health perspective, in turn supporting plans for an active aging.

Materials and Methods

A systematic, advanced search on PubMed, Scopus, and ISI Web of Science databases was conducted to identify studies published until the 2nd of September 2020, evaluating the possible relationship between shift or night work and the development of dementia. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria were followed[19]. The key terms used for our review were "shift work" or "night work" (including in this expression long working hours and any other atypical or antisocial work schedule too) to assess the exposure context, and "dementia" as the outcome of the investigation. The terms were combined with the Boolean operator "AND". All the titles and abstracts of the articles retrieved through the computerized search were independently examined by two of the authors. Papers suitable for the review purposes were selected according to the inclusion criteria. These included all types of human peer-reviewed research articles (i.e., descriptive epidemiological-occupational surveys, cross-sectional, cohort, case-control studies, case series) published in English, and reporting possible implications of shift or night work on various cognitive outcomes in different, real, occupational exposure scenarios. Studies published in languages other than English, reviews, case reports, conference papers, letters, notes, book chapters, editorials, experimental studies on cellular and animal models, as well as publications not specifically focusing on the cognitive function of shift workers or those that, although exploring cognitive outcomes, did not provide information on shift schedules, were excluded.

Results

Our preliminary research resulted in 23, 39 and 33 records identified through PubMed, Scopus, and ISI Web of Science databases, respectively, for a total of 95 articles. In all, 34 duplicates were removed, and 61 articles remained. Among those, 55 were excluded as they did not meet the inclusion criteria according to the following reasons: 33 were considered out of the topic from the title and abstract analysis; 10 were review articles; 4 were conference papers; 1 was a book chapter; 2 studies were removed as in languages other than English and 2 because conducted on animal models. Further 3 records excluded were a note, a letter and an editorial, respectively. Indeed, the full texts of all the articles (6) considered valuable for the aim of our review were obtained and subjected to a critical evaluation. The citation pool of relevant publications was enlarged through the analyses of the reference list accompanying

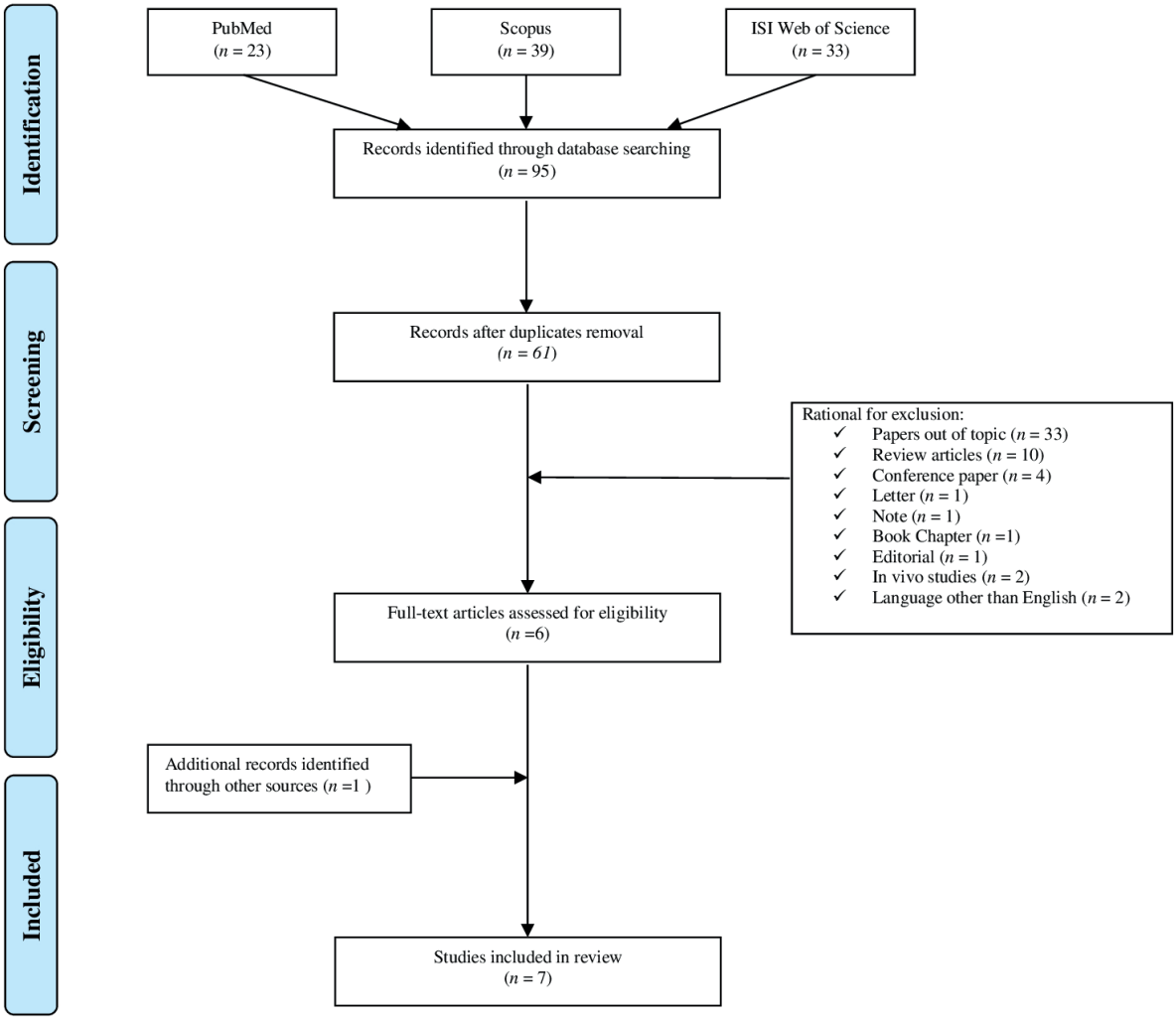

Figure 1. Flow diagram of literature search.

the selected articles. An additional eligible paper could be added. Overall, our search retrieved a total of 7 articles suitable for review (Figure 1).

The following section will attempt to summarize the currently available data concerning shift/night work relationships with the possible dementia manifestation in involved workers. Particular attention was paid to the influencing role of specific work schedules, diverse lenghts of employment in shift works, peculiar job tasks, and additional risk factors, including cardiovascular/metabolic comorbidities, unhealthy lifestyles, sleep parameters, and genotype (Table I).

Shift Work or Night Work and Risk of Dementia-Like Effects

Shift work of all schedule types as well as a night work history, compared to non-shift job, were associated with significantly higher dementia incidence, even when controlling for potential confounders, i.e., age, sex, education[20]. The association showed a slight attenuation upon adjustment for diabetes, cardiovascular disease and stroke, suggesting a possible mediating role of cardiometabolic disease. On the other hand, sleep parameters seem to not influence estimates of association between shift work and dementia. This was demonstrated by the higher incidence rate in shift workers of all types compared to night workers. A longer night shift work duration appeared to predict increased dementia rates, although with a modest dose-response association. Concerning the shift work duration, higher dementia rates were predicted by 1-9 and 10-19 years of work compared to no-shift works. On the other side, having 20 years or more of shift work was not

Table I. Summary of the studies addressing the relationship between shift work or night work and dementia.

Study location (year)	Investigated population	Outcome	Additional information	Results	Reference
Sweden (1973- 2008)	Cohort from the Swedish Twin Registry (STR) 1973: n. 13283; 6445M, 6838F; mean age±SD: 37.8±5.4 years). Cohort from the Screening Across the Lifespan Twin (SALT) sample (n. 41199; 19249M; 21950F; mean age±SD: 58.5±10.4 years)	Risk of incident dementia	*Diagnosis* Dementia diagnoses come from Swedish patient registries and were identified according to the International Classification of Disease (ICD) versions 8, 9 and 10 and the Anatomical Therapeutic Chemical Classification System (ATC) codes. *Occupational data* STR 1973 sample: shift workers (n. 2258); years in SW: 1-9 (74.7%); 10-19 (20.7%); ≥20 (4.6%). SALT-sample: night shift workers (n. 12399); years in night shift work: 1-9 (52.5%); 10-19 (22.3%); >20 (25.2%). *Clinical data* Genotyped individuals: n. 2977 in the STR 1973 sample (n. 931 APOE e4 carriers; n. 146 shift workers); n. 10366 in the SALT sample (n. 3140 APOE e4 carriers; 876 night shift workers)	Dementia incidence was significantly higher in shift workers compared to non-shift workers (fully adjusted models for age, sex, education, diabetes, cardiovascular disease and stroke) in the STR 1973 (HR 1.36, 95% CI 1.15-1.60) and in the SALT cohort (HR 1.12, 95% CI 1.01-1.23). APOEe4 carriers with ≥ 20 years of shift or night work had a significant increase in dementia risk than those never exposed to SW (HR 4.57, 95%CI 2.92-7.13 in STR sample; HR 2.07, 95% 1.25-3.44 in SALT sample).	Bokenberger et al[20]
Denmark (1993- 2013)	Nurses (n. 18015F)	All-cause and cause-specific mortality	*Clinical data* The Danish Register of Causes of Deaths was used to identify dementia deaths up to 2013 *Occupational data* SW: day shift (n. 11272; mean±SD age 50.2± 4.7 years); evening shift (n. 1805; mean±SD age 51.6 ± 5.5 years); permanent night shift (n. 980; mean±SD age 52.9±5.6 years); rotating-shift (n. 3958; mean±SD age 49.2±4.3 years).	Mortality from Alzheimer's disease or dementia (n. 33 deaths): significantly increased in nurses working evening (HR 4.28, 95% CI 1.62-11.3) and rotating (HR 5.39, 95% CI 2.35-12.3) shifts compared to those involved in day shifts. No significant association was found with night shifts (HR 0.70, 95% CI 0.09-5.72)	Jorgensen et al[22]

Table continued

Table I. ***(Continued).*** Summary of the studies addressing the relationship between shift work or night work and dementia.

Study location (year)	Investigated population	Outcome	Additional information	Results	Reference
Denmark (1993-2018)	Nurses from the Danish Nurses Organization (19898F; ≥ 44 years)	Incidence of dementia	*Clinical data* The Danish Registers were employed to obtain information on dementia hospitalization and prescription medication until 2018 *Occupational data* SW (cohort base-line 1993 or 1999): 62.6% of the nurses worked day shifts, 10.2% worked evening shifts, 5.5% worked night shifts, and 21.7% worked RSW	Nurses with one-point SW assessment in 1993 or 1999 (n.18892): a non-significantly higher dementia rate was determined among rotating shift workers (HR: 1.23, CI 95% 0.98-1.54). Nurses with repeated SW assessment in 1993 and 1999 (n. 6048): persistent night shift workers had a significantly higher risk of dementia (HR: 2.43; 95% CI: 1.39-4.23) than nurses with persistent day shifts. Nurses that completed the final cohort questionnaire in 2009 (n. 8059): a dose-response relationship was determined between duration of NSW and the rate of dementia for those working night shifts for 1-5 years and for ≥6 years, HR: 1.15; 95% CI 0.79-1.67 and HR: 1.46; 95%CI 1.05-2.03, respectively, when compared with nurses who worked NSW for < 1 year.	Jorgensen et al[23]
Denmark (1990- 2016)	Shift workers (n. 3339); workers for long working hours (n. 3414)	Risk of incident dementia	*Clinical data* Dementia diagnoses were obtained from the Danish national registers *Occupational data* SW: day workers (n. 2828; 50.2%; M 49.8%; mean±SD age 45.6±7.1years); shift workers-no NW (n. 396; F 49.5%; M 50.5%; mean±SD age 45.1±6.9 years); night shift workers (n. 115; F 56.5%; 43.5%; mean± age 45.4±7.6 years)	Dementia risk according to work schedule: non significantly increased in NSW (IRR: 2.01; 95% CI: 0.87-4.65), significantly increased in permanent night workers (IRR: 3.25; 95% CI: 1.35-7.83). SW without NW was not associated with a higher incidence of dementia. Dementia risk according to working hours/week: significantly increased in employees working 38-44 h/w (IRR:2.08; 95% CI: 1.11-3.90) compared to those working 37 h/w.	Nabe-Nielsen et al[24]

Table continued

Table I. ***(Continued).*** Summary of the studies addressing the relationship between shift work or night work and dementia.

Study location (year)	Investigated population	Outcome	Additional information	Results	Reference
Denmark (1970- 2014)	Employees (n. 4766M)	Risk of incident dementia	*Clinical data* Dementia diagnoses were obtained from the Danish national registers *Occupational data* Shift workers (n. 1011; mean±SD age 48.4±5.2 years); no shift workers (n. 3720; mean±SD age 49.1±5.4 years) Workers ≤45h/week (n. 3895; mean±SD age 49.1±5.4 years); workers ≥45 h/week (n. 869; mean±SD age 48.4±5.2 years).	Dementia risk: no significant association with SW (IRR 0.86, 95% CI 0.70-1.05) or long working hours (IRR 0.97, 95% CI 0.79-1.19).	Nabe-Nielsen et al[26]
Germany (1998- 2000)	Patients with dementia (n. 195; 44M; 151F; mean age±SD: 79.5± 8.4 years.	Risk of incident dementia	*Clinical data* Dementia diagnoses were recruited from 23 general practices in 1998- 2000. Patients with Alzheimer's dementia (n. 108); vascular dementia (n. 59); secondary or unclassified dementia (n. 28) *Occupational data* Working time arrangements was based on the Quality and Working Life Survey responses to one question concerning the exposure to different working time schedules, with emphasis on night work	Working time arrangements (SW or NW) were neither significantly associated with dementia in general nor with any specific type of dementia.	Seidler et al[25]
The Netherlands	Maritime pilots (n. 50M; mean age±SD 71.7±7.7 years).	Cognitive function	*Occupational data* Enrolled subjects had a history of > 25 years of work on irregular schedule (mean±SD years: 26±3)	No evidence of cognitive decline was repoted. The scores of the CFQ (cognitive functioning) and EDQ (early dementia symptoms) questionnaires were within the normal range.	Thomas et al[27]

CFQ, Cognitive Failure Questionnaire; EDQ, Early Dementia Questionnaire; NSW, night shift work; NW, night work; RSW, rotating shift work; SW, shift work.

significantly predictive of dementia, perhaps due to the smaller sample having extensive shift work history. Interestingly, considering that previous research suggested a possible association between sleep deprivation and Alzheimer's disease, a dementia subtype for which old age and the apolipoprotein E (APOE) ε4 allele are among the strongest risk factors[21], the relationship between shift- or night work and dementia incidence was assessed in genotyped subsamples by stratifying on APOE ε4- status. A significantly higher risk of dementia was observed in genetically susceptible individuals as APOE ε4-carriers compared to non carriers, and particularly in those exposed to ≥20 years of shift work and night work compared to day workers.

These results are in line with those obtained by a cohort study exploring the impact of shift work on cause-specific mortality in a sample of Danish nurses[22]. This investigation showed, in fully adjusted models, a significantly positive association between rotating (alternating between day, evening or night shifts) and evening shift work with mortality from AD and dementia's other subtypes. On the contrary, there was no evidence of an association between working night shifts and Alzheimer's or dementia. However, caution should be applied in the interpretation of these findings. In fact, these were based on a limited number of cases, 33 deaths in total, and a crude exposure information, assessed only at one point in time on a period of up to 14 years of follow-up. Additionally, a poorer survival among shift workers with dementia may not necessarily support a higher incidence of the disease in this group, considering also a possible influencing role of age on the work schedule performed. In fact, nurses in the younger age groups were more likely employed in rotating and night shifts, while older nurses more often worked in day or evening shifts. In addition, the strongest association found between Alzheimer's and other subtypes of dementia among rotating shift workers may suggest the relevance of additional mechanisms independent from circadian disruption. Possibly, stress-related insults occurring in nurses may play a role in dementia related mortality[22].

A following investigation from the same group[23] deeplier examined the association between the type of shift work schedule and its duration with the incidence of dementia in a sample Danish nurses. This study used detailed exposure information assessed at three different time points in 1993, 1999, and 2009. The authors found a significant positive association between permanent night shift work or night shift work for at least 6 years and risk of dementia, but none with other shift work schedules or shorter duration of night shift work. In addition, nurses who developed dementia were older, more often current smokers, part time workers, and reported moderate alcohol consumption and sleep medications' use compared to dementia-free nurses. Nurses with pre-existing cardiovascular disease or diabetes also seemed to be more susceptible to night shift work, with respect to developing dementia. The findings of an increased dementia rate among persistent night shift workers agree with a previous Danish study[24]. This detected a significantly higher dementia incidence only in this specific category of workers. The estimated differences were not explained by differences in baseline duration of vocational education, psychosocial work factors and lifestyle-related cardiovascular risk factors, therefore supporting the possible causal role of such specific work schedule in determining dementia risk[24].

In contrast to the above-mentioned results, additional literature evidence did not provide support to a possible association between shift work and dementia. Seidler et al[25] reported no significative association between shift/night work history with dementia in general nor with any specific type of the disease, i.e., Alzheimer's disease, vascular, secondary or unclassified dementia. This same case-control study investigated the relationship with psychosocial workplace factors, showing decreased dementia's odds ratios for very challenging work with high control possibilities and high social demands. No substantial differences could be detected between Alzheimer's disease and vascular dementia. Working under high perceived risks for error was, instead, associated with increased diagnosis of dementia in general, as well as with Alzheimer's disease and vascular dementia alone. Finally, psychosocial work factors, such as social climate at work, workload, supervisor support, and working time arrangements were neither significantly associated with dementia in general, nor with any specific type of dementia.

Similarly, the study performed by Nabe-Nielsen et al[26] did not find evidence of a statistically significant relationship between shift work or long working hours, ≥45 hours/week, and incident dementia. In this investigation, comparated to no shift workers, shift workers also had a poorer dementia risk factor profile in terms of sleep, work stress, smoking, and BMI. Conversely, they

had a better profile in term of leisure-time stress, cardiovascular disease, physical activity during leisure-time, and age. The most profound difference between the groups tested related to the lower socioeconomic position among shift workers *vs.* non-shift workers.

Thomas et al[27] performed an explorative, observational study investigating the possible relationship between long-term occupational sleep loss and post-retirement cognitive decline or dementia in a sample of retired maritime pilots and found neither evidence of cognitive complaints nor early dementia signs.

Discussion

This review represents the first attempt to comprehensively assess the possible impact of shift or night shift work on dementia development. Although the limited number of available studies and their not homogenous results do not allow to extrapolate definite conclusions, some critical aspects, that need further investigation, could be pointed out.

Some of the reviewed studies reported a significantly positive association between shift work and incident dementia[20,23,24], and mortality for dementia[22] compared to non-shift works. However, other investigations failed to achieve comparable findings[25-27]. Concerning schedule types, a couple of studies reported a significant association between permanent night shift works and dementia[23,24], while other investigations detected a positive relationship with all the schedule patterns[20], rotating[22], or fixed evening shift work examined[22].

These latter findings are contrary to the idea that night shift works, through greater circadian disturbances and sleep quality impairment, may be associated with a higher dementia risk compared to day and evening work[20,22]. The lack of the association between work-related sleep loss and dementia risk, could be influenced by the protective role of specific work schedule. In Thomas et al[27], in fact, the authors suggested that the adverse cognitive effects of sleep loss during a work-week could be counteracted by the rest periods during week off, when maritime pilots could recover and reverse the potential detrimental insults. Moreover, a possible "healthy worker" effect may be responsible for the lack of the association between shift- and night shift works and dementia development. In essence, aging, together with physical status and basal cognitive conditions of the employees, may determine the selection of healthy subjects into job types encompassing certain work schedules[22,26].

Concerning the role of the length of shift work employment in determining dementia-related effects, long-term exposure to any shift work patterns[20], as well as to night shift work[23], has been described as responsible for cognitive damaging effects on workers until dementia development. Indeed, during the occupational life, short duration of shift or night shift work, changing between different types of schedules, i.e., fixed day and shift work, may provide a healthier alternative to persistent night- or shift work with respect to reducing the dementia risk.

The main pathogenetic mechanism underlying the association between shift-work, including night work, and cognitive deterioration has been thought to be the repeated desynchronization of body clock due to working and sleeping at the wrong circadian phase in exposed workers[28-32]. This may determine disruptive effects on health, such as sleep deprivation, daytime sleepiness and brain inflammation that may overall increase vulnerability to age-related cognitive decline[24-26,33-37]. However, the association between dementia and work schedule types, different from night shifts, suggests that mechanisms other than circadian misalignment, may contribute to such vulnerability. In this context, it cannot be excluded that cardiometabolic morbidities, unhealthy lifestyles, as well as psychological stress associated with shift works, may play a mediating role in cognitive decline[13-18,38]. In this regard, the psychological stress induced by the disruption in the circadian rhythm due to night shift work has been suggested to have an adverse impact on brain structures involved in higher cognitive functions[39-41].

From an occupational health perspective, this underlines the need to clarifty the complex interplay between different occupational risk factors, i.e. shift works and psychosocial risks, but also chemical and not-occupational exposures, in possibly enhancing the risk for dementia development. This may explain the differences in the disease incidence found in nurses cohorts[20,22-24], which may experience also great levels of physocial risks while performing their tasks, compared to populations employed in different job sectors, i.e., maritime pilots[27], or groups of employees for which no details concerning specific occupational tasks have been provided[26]. Additionally, sleep loss may represent an early manifestation of neurodegenerative diseases or an early manifestation

of a disease that harbors an increased risk for dementia. These theories could explain why sleep loss, due to an extrinsic cause, like shift works, my not lead to an increased disease incidence, thus requiring to exclude a possible reverse causality and clearly define the impact of night shift work on cognitive decline.

Concerning genetic susceptibility to the adverse impact of shift work, only one study could demonstrate that the expression of the APOE ε*4* allele, which is the main genetic determinant of Alzheimer's disease, synergistically combine with other risk factors in contributing to significantly increase the risk of dementia and strengthening the dose-response association between shift or night work length and dementia risk[20]. However, the scientific evidence available about the regulating role of the circadian rhythm in the production of the amyloid beta peptide, as an essential component of the senile plaques hallmarks of the Alzheimer's disease[42-46], the synthesis of melatonin as a neuroprotective hormone[47-49], as well as about the neuroinflammation, oxidative stress and synaptic damage induced by sleep-awake cycle disruption[50], suggests the need for future investigations on biological alterations that may function as possible biomarkers for neurocognitive decline.

Overall, some limitations of the currently available studies should be overcome in future investigations. First of all, those concerning the measurement of the main occupational exposures. The ever shift work, and night work assessment represents a crude evaluation of a more complex work organization. Further studies, in this sense, should differentiate between rotating and fixed shifts, work schedules and their regularity/irregularity, recovery periods, lengths of employment in shift works, and peculiar job tasks. This may allow to better define how work shift features may differently impact on the neurocognitive decline. Secondarily, most of the available studies were performed in the Northern Europe. This may characterize a possible bias in the interpretation of the obtained results due to some specific conditions that may be experienced in such places compared to other European and worldwide countries. These may include the longer life expectancy[51], the possible different organization of the healthcare systems and the use of national registers, based on inpatients and outpatients care records, as a source of dementia data that may underestimate diagnoses performed only at the primary care level.

Considering that dementia currently affects around 10 million people in Europe and that its prevalence is expected to double by 2030[51], countries should recognize, such disorder as a public health priority. This should provide stimulus for greater research aimed to define the disease pathogenesis and influencing factors with the aim to achieve an early diagnosis and comprehensive treatment. In this view, tests able to determine preclinical alterations in, i.e., verbal memory, selective and sustained attention, reaction time, mental speed, and learning functionality should be aimed to identify reversible cognitive disorders in a preventive medicine perspective. In fact, to assess the relationship between shift, night work and dementia development fails to detect all the early cognitive alterations that may characterize the exposure disease continuum. This may limit the adoption of early preventive measures.

Conclusions

In summary, further research should be focused on confirming the association between shift and night works, and neurocognitive dysfunction. This may provide guidance to develop effective strategies for workplace risk assessment process, and lifestyle and occupational measures for disease prevention. These may include to appropriately organize work-shift schedules according to ergonomic criteria, i.e., to limit night work as much as possible; to avoid large number of consecutive nights; to prefer quickly and clockwise rotations; to set adequate number of rest days between shift; to keep the shift system as regular as possible allowing work time arrangements according to worker's needs and preferences[53-56]. Suitable information plans on possible effects of shift works on cognitive functions should be developed for employers and employees. Additionally, adequate health surveillance programs and social support for shift workers should be defined. These may allow subjects to keep working without significant impairment of their cognitive performance during their working life, but also after retirement, therefore supporting the "active aging" of the workforce and benefits for the public health system.

Funding

This research received no external funding.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia. JAMA 2019; 322: 1589-1599.
2) Scott KR, Barrett AM. Dementia syndromes: evaluation and treatment. Expert Rev Neurother 2007; 7: 407-422.
3) American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Publishing; 2013.
4) Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med 2014; 30: 421-442.
5) Hebert L, Scherr P, Bienias J, Bennett D, Evans D. Alzheimer disease in the US population: prevalence estimates using the census. Arch Neurol 2003; 60: 1119-1122.
6) Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jönsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016; 15: 455-532.
7) Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013; 9, 63.e2-75.e2.
8) Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015; 11: 718-726.
9) Killin LO, Starr JM, Shiue IJ, Russ TC. Environmental risk factors for dementia: a systematic review. BMC Geriatr 2016; 16: 175.
10) ILO, International Labour Office. Shift Work. Conditions of Work and Employment Programme. Information Sheet No. WT-8 2004. Available at https://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---travail/documents/publication/wcms_170713.pdf. Accessed on 22 September 2020.
11) Your Europe - European Union. Working hours. Available at: https://europa.eu/youreurope/business/human-resources/working-hours-holiday-leave/working-hours/index_en.htm#shortcut-5. Accessed on 22 September 2020.
12) Leso V, Vetrani I, Sicignano A, Romano R, Iavicoli I. the impact of shift-work and night shift-work on thyroid: a systematic review. Int J Environ Res Public Health 2020; 17: 1527.
13) Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang YF. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health 2014; 14: 643.
14) Puttonen S, Härmä M, Hublin C. Shift work and cardiovascular disease--pathways from circadian stress to morbidity. Scand J Work Environ Health 2010; 36: 96-108.
15) van der Hulst M. Long work-hours and health. Scand J Work Environ Health 2003; 29: 171-188.
16) Ju YES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology-a bidirectional relationship. Nat Rev Neurol 2014; 10: 115-119.
17) Sallinen M, Kecklund G. Shift work, sleep, and sleepiness-differences between shift schedules and systems. Scand J Work Environ Health 2010; 36: 121-133.
18) Virtanen M, Ferrie JE, Gimeno D, Vahtera J, Elovainio M, Singh-Manoux A, Marmot MG, Kivimäki M. Long working hours and sleep disturbances: the whitehall II prospective cohort study. Sleep 2009; 32: 737-745.
19) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.
20) Bokenberger K, Sjölander A, Dahl Aslan AK, Karlsson IK, Åkerstedt T, Pedersen NL. Shift work and risk of incident dementia: a study of two population-based cohorts. Eur J Epidemiol 2018; 33: 977-987.
21) Liao F, Yoon H, Kim J. Apolipoprotein E metabolism and functions in brain and its role in Alzheimer's disease. Curr Opin Lipidol 2017; 28: 60-67.
22) Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. Shift work and overall and cause-specific mortality in the Danish nurse cohort. Scand J Work Environ Health 2017; 43 117-126.
23) Jørgensen JT, Hansen J, Westendorp RGJ, Nabe-Nielsen K, Stayner LT, Simonsen MK, Andersen ZJ. Shift work and incidence of dementia: a Danish Nurse Cohort study. Alzheimers Dement. In press.
24) Nabe-Nielsen K, Hansen ÅM, Ishtiak-Ahmed K, Grynderup MB, Gyntelberg F, Islamoska S, Mortensen EL, Phung TKT, Rod NH, Waldemar G, Westendorp RGJ, Garde AH. Night shift work, long working hours and dementia: a longitudinal study of the Danish Work Environment Cohort Study. BMJ Open 2019; 9: e027027.
25) Seidler A, Nienhaus A, Bernhardt T, Kauppinen T, Elo AL, Frölich L. Psychosocial work factors and dementia. Occup Environ Med 2004; 61: 962-971.
26) Nabe-Nielsen K, Garde AH, Ishtiak-Ahmed K, Gyntelberg F, Mortensen EL, Phung TKT, Rod NH, Waldemar G, Westendorp RG, Hansen ÅM. Shift work, long working hours, and later risk of dementia: a long-term follow-up of the Copenhagen Male Study. Scand J Work Environ Health. 2017; 43: 569-577.
27) Thomas J, Overeem S, Claassen JAHR. Long-term occupational sleep loss and post-retirement cognitive decline or dementia. Dement Geriatr Cogn Disord 2019; 48: 105-112.

28) Marquié JC, Tucker P, Folkard S, Gentil C, Ansiau D. Chronic effects of shift work on cognition: findings from the VISAT longitudinal study. Occup Environ Med 2015; 72: 258-264.
29) Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. Curr Alzheimer Res 2013; 10: 767-775.
30) Costandi M. Neurodegeneration: amyloid awakenings. Nature 2013; 497: S19-20.
31) Costa G. Shift work and health: current problems and preventive actions. Saf Health Work 2010; 1: 112-123.
32) Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med 2003; 53: 89-94.
33) Khan S, Duan P, Yao L, Hou H. Shiftwork-mediated disruptions of circadian rhythms and sleep homeostasis cause serious health problems. Int J Genomics 2018; 2018: 8576890.
34) Costa G. The impact of shift and night work on health. Appl Ergon 1996; 27: 9-16.
35) Rouch I, Wild P, Ansiau D, Marquie JC. Shiftwork experience, age and cognitive performance. Ergonomics 2005; 48: 1282-1293.
36) Devore EE, Grodstein F, Schernhammer ES. Shift work and cognition in the Nurses' health study. Am J Epidemiol 2013; 178: 1296-1300.
37) Vetter C, Devore EE, Ramin CA, Speizer FE, Willett WC, Schernhammer ES. Mismatch of sleep and work timing and risk of type 2 diabetes. Diabetes Care 2015; 38: 1707-1713.
38) Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab 2016; 36: 172-186.
39) Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 2009; 10: 434-445.
40) Li L, Wu M, Liao Y, Ouyang L, Du M, Lei D, Chen L, Yao L, Huang X, Gong Q. Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. Neurosci Biobehav Rev 2014; 43: 163-172.
41) Zheng C, Quan M, Yang Z, Zhang T. Directionality index of neural information flow as a measure of synaptic plasticity in chronic unpredictable stress rats. Neurosci Lett 2011; 490: 52-56.
42) Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009; 326: 1005-1007.
43) Roh JH, Huang Y, Bero AW, Kasten T, Stewart FR, Bateman RJ, Holtzman DM. Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. Sci Transl Med 2012; 4: 150ra122.
44) Bateman RJ, Wen G, Morris JC, Holtzman DM. Fluctuations of CSF amyloid-beta levels: implications for a diagnostic and therapeutic biomarker. Neurology 2007; 68: 666-669.
45) Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M, Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: a randomized clinical trial. JAMA Neurol 2014; 71: 971-977.
46) Huang Y, Potter R, Sigurdson W, Santacruz A, Shih S, Ju YE, Kasten T, Morris JC, Mintun M, Duntley S, Bateman RJ. Effects of age and amyloid deposition on Aβ dynamics in the human central nervous system. Arch Neurol 2012; 69: 51-58.
47) Kostoglou-Athanassiou I. Therapeutic applications of melatonin. Ther Adv Endocrinol Metab 2013; 4: 13-24.
48) Meliska CJ, Martinez LF, Lopez AM, Sorenson DL, Nowakowski S, Parry BL. Relationship of morningness-eveningness questionnaire score to melatonin and sleep timing, body mass index and atypical depressive symptoms in peri- and post-menopausal women. Psychiatry Res 2011; 188: 88-5.
49) Dumont M, Benhaberou-Brun D, Paquet J. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. J Biol Rhythm 2001; 16: 502-511
50) Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. Exp Mol Med 2015; 47: e148.
51) World Health organization, WHO. Global Health Observatory (GHO) data. Life expectancy. https://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends_text/en/. Accessed on 22 September 2020.
52) World Health organization- Europe, WHO-Europe. Dementia. Available at https://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/areas-of-work/dementia. Accessed on 22 september 2020.
53) Knauth P. Designing better shift systems. Appl Ergon 1996; 27: 39-44.
54) Knauth P. Innovative worktime arrangements. Scand J Work Environ Health 1998; 24 Suppl 3: 13-17.
55) Gärtner J, Popkin S, Leitner W, Wahl S, Akerstedt T, Folkard S. Analyzing irregular working hours: lessons learned in the development of RAS 1.0--The Representation and Analysis Software. Chronobiol Int 2004; 21: 1025-1035.
56) Costa G, Sartori S, Akerstedt T. Influence of flexibility and variability of working hours on health and well-being. Chronobiol Int 2006; 23: 1125-1137.