

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Night shift work, long working hours and dementia: A longitudinal study of the Danish Work Environment Cohort Study
AUTHORS	Nabe-Nielsen, Kirsten; Hansen, Åse Marie; Ishtiak-Ahmed, Kazi; Grynderup, Matias; Gyntelberg, Finn; Islamoska, Sabrina; Mortensen, Erik; Phung, Thien; Hulvej Rod, Naja; Waldemar, Gunhild; Westendorp, Rudi; Garde, Anne

VERSION 1 – REVIEW

REVIEWER	Christian Benedict Uppsala Universitet
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	<ol style="list-style-type: none">1. You wrote: Additionally, observational studies support an association between disturbed sleep and dementia. Please cite here the two following studies: PMID 25438949 & 300301122. Are shift workers with longer work hours per week at increased risk for dementia compared with shift workers with standard or short work hours per week? In my view, you should adjust the shift work analysis for working hours, and vice versa. For instance, do you still see the association between working moderately longer than the standard weekly working hours and the risk of dementia when adjusting for type of shift work (ie., day work; shift work(-night shift work; and shift work (+night shift work))?3. You wrote: Permanent night work analyzed separately: IRR=3.49; 95% CI: 1.46-8.32 (model 1). Did you also observe this association between permanent shift work and dementia risk in the models 2 and 3?4. You refer to sleep disturbances as a possible mediator of the association between shift work/long workweeks and dementia? With this in mind, please show these data in Table 1. Did you adjust your analyses for sleep disturbances? According to table 2, model 2 was adjusted for Model 1 + ruminations about work, influence at work, and possibilities for development. Sleep is however not mentioned here. Please clarify!
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REVIEWER	Tomoyuki Ohara, M.D., Ph.D Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
REVIEW RETURNED	20-Oct-2018

GENERAL COMMENTS	This paper explores the association between shift work and long working hours and risk of dementia using register-based measures of dementia. The objective of this study is interesting, however, there are some issues to be concerned of the methodology of this
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	<p>study (e.g. study population selection, follow-up methods, interpretation of data).</p> <ol style="list-style-type: none"> 1. Target population is unclear, although the authors commented the exclusion criteria. The authors should clarify how target subject selected using a flow chart of the study participants excluded at baseline. 2. Follow-up method of this study is unclear. From when did the target subjects start to follow-up? I am wondering this study explored the association of midlife shift work and risk of late life dementia. Is this correct? 3. In the Methods section, the authors commented the subtypes of dementia. However, no results of the association with the risk of dementia subtypes were found probably due to the small number of event cases. I think the incidence rate of dementia of this study is relatively low regardless of the using register-based measures of dementia. Is there any problem of the selection of the study participants (selection bias including younger subjects)? Since statistical power of this study is too low to elucidate the true association between shift work and long working hours and risk of dementia, the authors should comment about this point.
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Christian Benedict

Institution and Country: Uppsala Universitet

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

1. You wrote: Additionally, observational studies support an association between disturbed sleep and dementia. Please cite here the two following studies: PMID 25438949 & 30030112

Response:

The following studies are included as reference supporting the association between disturbed sleep and dementia:

- Benedict et al.: Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimer's & Dementia* 2015
- Sindi et al. Sleep disturbances and dementia risk: A multicenter Study. *Alzheimer's & Dementia* 2018

To prevent an excessive amount of references, we have omitted:

- Lim et al: Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep* 2013

2. Are shift workers with longer work hours per week at increased risk for dementia compared with shift workers with standard or short work hours per week? In my view, you should adjust the shift work analysis for working hours, and vice versa. For instance, do you still see the association between working moderately longer than the standard weekly working hours and the risk of dementia

when adjusting for type of shift work (ie., day work; shift work(-night shift work; and shift work (+night shift work))?)

Response: The distribution of shift work among the different categories of weekly working hours and vice versa is presented in Table 1 in order to give the reader the possibility to assess the degree of confounding.

The combination of long working hours and shift work cannot reliably be estimated because of a very low number of participants and cases in some cells. In particular, night shift workers seldom worked moderately longer hours (n=9; 8%) or long hours (n=7; 7%). Thus, night workers are overrepresented among those with shorter working hours (28-36 h/w), and participants with moderate longer working hours predominantly worked day shifts (n=305; 87%).

We have added the following text to the results section:

“Furthermore, when mutually adjusted, the IRR for dementia was 1.83 (95% CI: 0.96-3.49) among those working 38-45 h/w and 1.86 (95% CI: 0.79-4.38) for night shift workers (also adjusted for gender, age, time since exposure assessment, calendar year, and duration of vocational education).”

3. You wrote: Permanent night work analyzed separately: IRR=3.49; 95% CI: 1.46-8.32 (model 1). Did you also observe this association between permanent shift work and dementia risk in the models 2 and 3?

Response: We have added the estimates for model 2 and 3 in the table notes:

“†) Permanent night work analyzed separately: IRR=3.48; 95% CI: 1.46-8.30 (model 1), IRR=3.58; 95% CI: 1.50-8.57 (model 2), IRR=3.91, 95% CI: 1.66-9.21 (model 3).”

4. You refer to sleep disturbances as a possible mediator of the association between shift work/long workweeks and dementia? With this in mind, please show these data in Table 1. Did you adjust your analyses for sleep disturbances? According to table 2, model 2 was adjusted for Model 1 + ruminations about work, influence at work, and possibilities for development. Sleep is however not mentioned here. Please clarify!

Response: Unfortunately, we do not have information about sleep disturbances as such. We can approximate this variable by the question “Do you have difficulties falling asleep, because of ruminations about your work?”. This variable is presented as an indicator of psychological work stress and presented in Table 1 and included in Table 2, model 2.

Reviewer: 2

Reviewer Name: Tomoyuki Ohara, M.D., Ph.D

Institution and Country: Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This paper explores the association between shift work and long working hours and risk of dementia using register-based measures of dementia. The objective of this study is interesting, however, there are some issues to be concerned of the methodology of this study (e.g. study population selection, follow-up methods, interpretation of data).

1. Target population is unclear, although the authors commented the exclusion criteria. The authors should clarify how target subject selected using a flow chart of the study participants excluded at baseline.

Response: We have added a flow-diagram that illustrates the process of selecting participants who were eligible for inclusion (Figure 1). In order to develop this flow-diagram, we employed a more fine-grained and individualized start of follow-up, i.e. from the month that the participant turned 60 years instead of starting from the calendar year following the participant's 60 year's birthday. This change implied that we included an additional sample of 188 participants who turned 60 years during 2016, and it also explains the small changes in the presented estimates and in the number of person-years. The results and conclusion remain unchanged.

We have also revised the description of the selection of participants and the design of the study:

“We used survey data from each participant's first participation in DWECs (i.e. 1990 or 1995). We only included participants who turned 60 years during the study's follow-up period, which ended 31st of December 2016. Thus, only participants born in 1956 or earlier were eligible for inclusion. The reason was that dementia diagnoses registered among younger patients have shown to be unreliable compared with dementia diagnoses in older patients²⁶⁻²⁸. Furthermore, to reduce the risk of reverse causation, i.e. that the often prolonged, subclinical phase of dementia affected selection into/out of shift work and long weekly working hours, only participants who were alive, not emigrated and free of dementia during the first five years after participating in the survey were eligible for inclusion (Figure 1). The design of the study is depicted in Figure 2.

To be included in the study, participants had to have provided valid information about the duration of their education, whether they had shift work and/or the number of weekly working hours. In total, 41 participants were missing on education. A large number of participants were missing on shift work and working hours (n=1518) mainly because they were out of the labor market at the time of the survey (e.g. unemployed or on disability pension).

After applying these criteria, the final sample consisted of 3339 participants for the analyses of shift work and 3414 participants for the analyses of long working hours.”

2. Follow-up method of this study is unclear. From when did the target subjects start to follow-up? I am wondering this study explored the association of midlife shift work and risk of late life dementia. Is this correct?

Response: It is correct that we used information about shift work and weekly working hours from midlife. When the participants filled in the questionnaire, the mean age was between 44.3 and 47.3 years in the applied exposure groups (Table 1). Outcome information was obtained from registers. We started the inclusion of risk time when two criteria were fulfilled: The participant should have turned 60 and at least 5 years after exposure assessment should have passed. To illustrate this, we have included a figure describing the design (Figure 2).

(The letters in the following comments are added by the authors in order to ease the reading of the response.)

3. In the Methods section, the authors commented the subtypes of dementia. **(a)** However, no results of the association with the risk of dementia subtypes were found probably due to the small number of event cases. **(b)** I think the incidence rate of dementia of this study is relatively low regardless of the using register-based measures of dementia. Is there any

problem of the selection of the study participants (selection bias including younger subjects)?
(c) Since statistical power of this study is too low to elucidate the true association between shift work and long working hours and risk of dementia, the authors should comment about this point.

a) We have added the following explanation to the discussion of strengths and limitations of the study:

“Yet, we did not analyze subtypes of dementia, e.g. Alzheimer’s disease. First, the validity of the subtypes in the Danish registries seems to be poor²⁵. Second, we did not hypothesize that the effect of night shift work was restricted to one specific dementia subtype. Third, the statistical power of our study did not allow for more nuanced analyses.”

b) This is indeed a reasonable point. We have added the following comment to the Discussion:

“The use of a register-based outcome has the advantage of a negligible loss to follow-up, although there is an underreporting of dementia in the general population³³. Indeed, even when taking into account that the maximum age at the end of follow-up of the included participants, the dementia incidence seemed to be relatively low (2.6 per 1.000 person-years) compared with the corresponding figures for Western Europe (60-64 years: 3.1; 65-69 years old: 5.3; 70-79 years’ old: 9.3)⁴⁶. As we only included participants who were employed at the time of the exposure assessment, our sample is likely to be healthier than the Danish population in general. In addition, underdiagnosis or diagnosis in primary care, which is not captured in the national registers, may contribute to the observed incidence rate.”

c) In the conclusion, we have now explicitly emphasized the insufficient statistical power:

“The study suffered from insufficient statistical power due to the small number of participants exposed to night work and the small number of dementia cases. Therefore, this is a cautious conclusion, which needs to be substantiated in future studies.”

VERSION 2 – REVIEW

REVIEWER	Christian Benedict Uppsala Universitet
REVIEW RETURNED	15-Jan-2019
GENERAL COMMENTS	No additional comments.
REVIEWER	Tomoyuki Ohara, M.D., Ph.D Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
REVIEW RETURNED	19-Jan-2019
GENERAL COMMENTS	The authors have satisfactorily responded to all my questions and made the necessary changes to the manuscript.