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Abstract

Objective:

To investigate the associations between midlife work-related stress and mild cognitive impairment (MCI), dementia and Alzheimer's disease later in life, in a large representative population.

Methods:

CAIDE study participants were randomly selected from independent population-based surveys (mean age 50). A random sample of 2,000 individuals was invited for two re-examinations including cognitive tests (at mean age 71 and mean age 78), and 1511 subjects participated in at least one re-examination (mean follow-up 28.5 years). Work-related stress was measured using two questions on work demands, which were administered in midlife. Analyses adjusted for important confounders.

Results:

Higher levels of midlife work-related stress were associated with higher risk of MCI [odds ratio OR, 1.38; 95% confidence interval (CI), 1.08–1.76], dementia [OR, 1.53; CI, 1.13-2.07], and Alzheimer's disease [OR, 1.55; CI, 1.19–2.36] at the first follow-up among the CAIDE participants. Results remained significant after adjusting for several possible confounders. Work-related stress was not associated with MCI and dementia during the extended follow-up.

Discussion:

Midlife work-related stress increases the risk for MCI, dementia, and Alzheimer's disease in later life. The association was not seen after the extended follow-up possibly reflecting selective survival/participation, heterogeneity in dementia among the oldest-old and a critical time window for the effects of midlife stress.

Introduction

Psychological stress and elevations in stress hormones are associated with worse cognitive performance, and older adults are particularly vulnerable to these negative effects (Lupien et al., 1998; McEwen, 2007; Sindi, Fiocco, Juster, Pruessner, & Lupien, 2013). Older adults commonly experience stress in their daily lives due to life transitions such as retirement, changes in health, financial strain, and social networks (Krause N, 2008; van der Heide, van Rijn, Robroek, Burdorf, & Proper, 2013). Recent studies have reported that midlife self-reported general stress and psychosocial stressors are associated with an increased risk for dementia or Alzheimer's disease (Hakansson et al., 2009; Johansson et al., 2013; Johansson et al., 2010). Such findings highlight the importance of midlife stress and a life-course approach when investigating the impact of chronic stress on dementia risk (Mangialasche, Kivipelto, Solomon, & Fratiglioni, 2012).

Perceived stress peaks in midlife (Bergdahl, 2002), and one important midlife stressor is work-related stress, especially considering the vast amount of time individuals spend at work throughout their lifespan. Work-related stress is associated with various physical and mental health outcomes (Chandola, Brunner, & Marmot, 2006; Nilsen et al., 2014; Steptoe & Kivimaki, 2013; Wahrendorf et al., 2012). One of the most frequent models used to measure work-related stress is the job demand-control-support model (Karasek, 1979, Theorell & Karasek, 1996). This model is environmentally based and measures stress sources, e.g., work stressors. The model postulates that high job demands, low job control and the combination of those are associated with ill health, in both cross-sectional and longitudinal studies (Nieuwenhuijsen, Bruinvels, & Frings-Dresen, 2010).

Work-related stress in the form of low job control or high job strain is associated with worse cognition and cognitive decline (Andel, Crowe, Kareholt, Wastesson, & Parker, 2011; Andel et al., 2015; Elovainio et al., 2009); however, to our knowledge less than a handful of studies have explored the association between work-related stress and dementia. Some studies have investigated associations between midlife work-related stress and dementia in later-life according to this model. Both high job strain and low levels of job control were associated with higher dementia risk later in life (Wang, Wahlberg, Karp, Winblad, & Fratiglioni, 2012). Similarly, high levels of job control and high challenges were associated with a reduced risk for dementia (Seidler et al., 2004). Other studies demonstrated that low job control, low social support at work, and a higher number of stress-related physical symptoms are associated with increased dementia risk (Andel et al., 2012; Crowe, Andel, Pedersen, & Gatz, 2007), while higher job demands were not associated with increased risk for dementia in one study (Crowe et al., 2007), and in another study higher job demands were only associated with vascular dementia, not with other dementia types (Andel et al., 2012). Inconsistencies in the literature may be due to lack of statistical power in some studies, the duration until the assessment of dementia diagnosis and the nature of the stress measures, where some used self-reported measures while others used occupation-based measures.

Based on the existing literature, it still remains unclear whether self-reported increased job demands (as measured by an elevated work load and a hectic work-schedule) is associated with an increased risk for mild cognitive impairment, dementia, and Alzheimer's disease. In the current study, we have used a population-based cohort study to investigate the associations between midlife work-related stress and specifically job

demands, and the onset of dementia in later life as assessed during two re-examinations, where the average total follow-up was 28.5 years.

In the current study, we assess factors that could potentially modify the association between midlife work-related stress and late-life dementia, and we have included these factors as covariates. For example, increased age, low education levels, the Apolipoprotein E ε4 genetic allele, and vascular / metabolic risk factors are well-known risk factors for dementia (for a review see (Sindi, Mangialasche, & Kivipelto, 2015)). There are also some psychological factors that increase the risk for dementia, such as high levels of hopelessness (Hakansson, Soininen, Winblad, & Kivipelto, 2015), and high levels of loneliness (Holwerda et al., 2014; Wilson et al., 2007). Many of the risk factors for dementia are also associated with stress, for example vascular and metabolic conditions (Chandola et al., 2006; Steptoe & Kivimaki, 2013), hopelessness (Joiner, 2005) and loneliness (Aanes, 2009). Considering the multiple potential pathways when assessing the associations between work-related stress and dementia, we have included these factors as covariates in the analyses.

Materials and methods

Study population

Participants of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study were first examined at midlife (baseline) in the North Karelia Project and the FINMONICA study, where individuals were assessed in one of the following years for the baseline assessment: 1972, 1977, 1982 or 1987 in Finland (Puska, 2010). Baseline participation rates ranged between 82%-90%. In 1998, a random sample of 2000 survivors living in the cities of Kuopio and Joensuu, aged 65-79, were invited for a first

re-examination (Figure 1). A total of 1449 (72.5%) individuals participated and 1409

completed the cognitive assessments. The mean follow-up time was 21 years (SD = 4.9).

Participants returned for a second re-examination between 2005 and 2008. In 2005, of the

2000 original sample, 1426 were alive and were still living in the same region. When

invited, 909 (63.7 %) of these accepted to participate and 852 completed the cognitive

assessment. A total of 1511 individuals participated in at least one re-examination, and

750 participated in both. The following were the mean ages at each time point: At

baseline, 50 years (SD = 6.0, age range: 39-64); at the first re-examination, 71.3 years

(SD = 4.0, age range: 65-80); at the second re-examination, 78.6 years (SD = 3.7, age

range: 72-90). Local ethics committees approved the CAIDE study and participants

provided written informed consent. The study complies with the Declaration of Helsinki.

Measurement of work-related stress

Perceived work-related was measured in midlife using the two questions that focus on

'job demands', which were validated by Karasek and colleagues (Karasek, Baker,

Marxer, Ahlbom, & Theorell, 1981) and have been used reliably by various research

groups (Andel et al., 2011; Nilsen et al., 2014; Toivanen, 2011). Both questions have the

same 5-point likert scale. The questions asked, "How often do you struggle to cope with

the amount of work?" and "How often are you bothered by constant hurry at work?".

After reverse coding to facilitate the interpretation of the results, the response options

were: 1=never, 2=rarely, 3=sometimes, 4=often, 5=always. Data on work-related stress

was available for 1,431 participants and 442 non-participants.

Diagnosis of mild cognitive impairment, dementia and Alzheimer's disease in the CAIDE study

Cognitive performance was assessed in both re-examinations using a three-step protocol for dementia diagnosis: screening phase, clinical phase and differential diagnostic phase. At the first re-examination (1998), participants who scored ≤24 on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) at screening were referred to the clinical phase for further examinations. At the second re-examination in 2005-2008, participants with ≤24 points on MMSE, or with decrease ≥3 points on MMSE since 1998, or with <70% delayed recall in the consortium to establish a registry for Alzheimer's disease (CERAD) word list (The consortium to establish a registry for Alzheimer's disease [CERAD]) (Morris et al., 1989), or with informant concerns regarding the participant's cognition were referred to the clinical phase. These additional criteria were used to increase sensitivity and detect milder cognitive impairment. The clinical phase included detailed neurological, cardiovascular and neuropsychological examinations, and the differential diagnostic phase included brain imaging (Magnetic Resonance Imaging (MRI) / Computerized Tomography (CT)), blood tests, and if needed cerebrospinal fluid analysis, and electrocardiogram. A review board including the physician, neuropsychologist and a senior neurologist ascertained the primary diagnosis based on all information.

Dementia diagnosis was determined using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria . For diagnoses of Alzheimer's disease, the criteria used were those of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-

ADRDA) (McKhann et al., 1984). Mild cognitive impairment (MCI) was diagnosed

using a modified version of the Mayo Clinic Alzheimer's Disease Research Center

criteria (Petersen et al., 1997) which included the following criteria: (a) memory

complaint by patient, family, or physician, (b) preserved activities of daily living, (c)

normal global cognitive function, (d) objective impairment of memory or another

cognitive domain, as indicated by scores > 1.5 standard deviations below the age

appropriate normative mean, (e) clinical dementia rating score of 0.5 and (f) not

demented. No participants had dementia at baseline.

Diagnosis of dementia and Alzheimer's disease in registers

We obtained additional information on dementia diagnoses from the National Hospital

Discharge Register, which provides information on in-patients at public hospitals, as well

as the Drug Reimbursement Register and Causes of Death Register. Diagnoses in both

Hospital Discharge Register and Causes of Death Register are defined using International

Classification of Diseases (ICD) codes. Although dementia may be under-reported in

registers, diagnoses have been reported to be highly accurate in Finnish national registers.

When information on dementia and Alzheimer's disease diagnoses is obtained from all

three registers, the positive predictive value is above 90%, indicating high accuracy

(Solomon et al., 2014). In the Drug Reimbursement Register, the accuracy for

Alzheimer's disease is 97.1% with a sensitivity of 63.5%. In the Hospital Discharge

Register, sensitivities are 51% for dementia and 55.6% for Alzheimer's disease. When

data from the Hospital Discharge Register and Drug Reimbursement Register are

combined for Alzheimer's disease diagnoses, sensitivity increases to 71.1%, with a

positive predictive value of 100%. In the Causes of Death Register, sensitivity for dementia diagnoses is 62.2% and the accuracy is 100% (Solomon et al., 2014).

Other assessments

At baseline (midlife), assessments and survey methods were standardized and adhere to international guidelines and the World Health Organization (WHO) (Multinational MONItoring of trends and determinants in CArdiovascular disease) MONICA protocol ("Geographical variation in the major risk factors of coronary heart disease in men and women aged 35-64 years. The WHO MONICA Project," 1988). Re-examination surveys were similar and comparable to those at baseline. Baseline surveys involved self-administered questionnaires on medical history, sociodemographic factors, health status, health-related behaviors and psychological-related factors. We have selected the following covariates as they have been shown to be associated with an increased risk of dementia and/or high levels of stress: age, sex, education, APOE ε4, BMI, respiratory, cardio/cerebrovascular and musculoskeletal conditions, systolic blood pressure, cholesterol, type of occupation, smoking, cohabitant status, loneliness and hopelessness (as recently demonstrated by results using the CAIDE study (Hakansson et al., 2015).

We measured main lifetime occupation by asking individuals to select their longest-held occupation among the following categories: office/service, farming/forestry, mining/industrial/construction work, housewives, or other. Hopelessness was measured using two items that were identical to those in former studies on mortality, as described recently (Hakansson et al., 2015). The questions stated, "I feel that it is impossible to reach the goals I would like to strive for" and "The future seems to me to be hopeless,

and I cannot believe that things are changing for the better". A five-point Likert scale was used, coded as 0 = absolutely agree; 1 = somewhat agree; 2 = cannot say; 3 = somewhat disagree; or 4 = absolutely disagree. Loneliness was measured using the following question "I feel that I have no good friend", which also used a five-point Likert scale, coded as 0 = absolutely agree; 1 = somewhat agree; 2 = cannot say; 3 = somewhat disagree; to 4 = absolutely disagree.

A trained nurse verified the answers and addressed participants' questions. The nurse also measured height, weight and blood pressure. Body mass index (BMI) was calculated by dividing weight (kilograms) by height squared (meters). A venous blood sample was obtained, and allowed for measures of biomarkers, including cholesterol and APOE genotype from blood leucocytes, for which HHaI digestion and polymerase chain reaction were used . The Hospital Discharge Register was used for information on respiratory and cardio/cerebrovascular conditions (chronic obstructive pulmonary disease, asthma, coronary artery disease, stroke, myocardial infarction, atrial fibrillation, cardiovascular surgery, heart failure or diabetes). All covariates were measured at baseline.

Statistical analyses

We conducted analyses using Stata 13.0 (Stata Corp, College Station, TX, USA). We analyzed participant baseline characteristics using Chi square (x^2) tests for categorical variables (data reported as percentages), and Student t-tests for continuous variables (data reported as means (standard deviations [SD])). The significance level for all analyses was set at $p < 0.05$.

We performed analyses for the associations between midlife work-related stress and dementia among participants (N=1511), using dementia diagnoses from CAIDE examinations (Kulmala et al., 2014). We also performed sensitivity analyses using the entire target population (N=2000), where diagnoses from both CAIDE and registers were used.

Modeling of work-related stress

Prior to deciding how to model the stress variables, we first ascertained that both questions were highly correlated (Spearmans rho = 0.623, p < 0.001). We then combined both questions into a composite score and dichotomized the stress variable, where the first tertile (low stress, with a score ranging from 2-5) was compared to the second and third tertiles (moderate-high stress, with a score ranging from 6-10). Our results showed that higher levels of stress were associated with a higher risk for dementia (p = 0.017) and Alzheimer's disease (p = 0.005).

We were then interested in assessing whether the association was driven by both questions on stress, so we simultaneously included both questions (controlled for each other). Results showed that the variable based on the question "How often are you bothered by constant hurry at work?" was associated with dementia (p = 0.011) and Alzheimer's disease (p = 0.016), whereas the results based on the question "How often do you struggle to cope with the amount of work?" were not significantly associated with dementia (all p > 0. 47) or Alzheimer's disease (p > 0.70).

Subsequently, we performed two logistic regression analyses with dementia and Alzheimer's disease as outcomes, where we included both separate questions on stress as predictors given linear representation, in addition to all confounding factors listed in model 3 of the analyses (age, sex, follow-up time, education, BMI, occupation type, APOE4 genotype, cholesterol, smoking, systolic blood pressure, hopelessness, loneliness, cohabitant status, cardiovascular conditions). Interestingly, the results showed that only the question on constant hurry at work was associated with the risk for dementia ($p = 0.023$) and Alzheimer's disease ($p = 0.016$), whereas the question on the amount of work was not a significant predictor (all $p > 0.71$). Moreover, we performed analyses using dummy representation (dummy variables) to test if the associations where approximately linear or non-linear for each of the two questions. The results showed that the associations were approximately linear. Considering the high discrepancy in predictive value between the questions, we continued our analyses with the question on constant hurry only.

Analyses for CAIDE participants

To investigate the associations between the two questions related to midlife work-related stress and dementia until the first re-examination, we performed logistic regression analyses. We also used logistic regressions to assess the associations between midlife work-related stress and dementia between the first and the second re-examination. We reported results as odds ratios (OR) and 95% confidence intervals (CI). All analyses were adjusted for a basic set of confounders: age, sex, total years of education, follow-up time and ApoE ε4 allele (all included in Models 1 and 2). Subsequent analyses (Models 2) included additional adjustments for the following confounding factors measured in

midlife: BMI, systolic blood pressure, cholesterol, type of occupation (categorized as non-white collar occupations (farming / forestry, mining / industrial / construction work, housewives, and others) or white-collar jobs (office / service), smoking, cohabitant status (cohabitant / non-cohabitant), hopelessness and loneliness, respiratory, cardio/cerebrovascular conditions.

Additional analyses (entire CAIDE target population)

We obtained information on dementia diagnoses from the CAIDE re-examinations when data was available, while we used register diagnoses for non-available data (for cases of non-participants, non-survivors, or participants who had no dementia at first re-examination and did not return for the second re-examination). We carried out hazard regressions with Gompertz distributed baseline intensity (using the Streg function in Stata 13.0), with midlife age set as origin and censored age as time scale. For associations between midlife work-related stress and dementia until the first re-examination (1998), censoring was done at the end of 1998 or date of death of deceased. For associations between midlife work-related stress and dementia until the second re-examination (2005-2008), censoring was done at the end of 2008 or date of death if deceased before end of 2008. Results are reported as hazard ratios (HR) and 95% CI. Analyses in Models 1 and 2 adjusted for the same sets of confounding factors previously mentioned.

Results

Population characteristics

Table 1 shows sociodemographic and clinical characteristics of the entire CAIDE target population. Comparisons show that the non-participant group was older at the midlife

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assessment, had fewer years of formal education, higher levels of midlife work-related

stress, higher midlife BMI, higher midlife systolic blood pressure, higher midlife

cholesterol levels, were more likely to have non-white-collar occupations (farming /

forestry, mining / industrial / construction work, housewives, and others), were more

likely to live alone, had higher levels of midlife hopelessness and loneliness and had a

higher rate of dementia. Participants and non-participants did not differ in the distribution

of sex, carriers of the APOEε4 allele, smoking status, midlife cardio-/cerebrovascular

conditions and Alzheimer's disease.

Among the individuals who participated in at least one re-examination (1511), 61 were

diagnosed with dementia (48 with Alzheimer's disease) during the first re-examination,

and 62 received dementia diagnoses (52 with Alzheimer's disease) at the second re-

examination (total of 123 dementia cases). A total of 82 individuals were diagnosed with

MCI in the first re-examination, and 131 were diagnosed with MCI in the second re-

examination (total of 213 MCI cases).

Midlife work-related stress and risk of dementia

Associations between midlife work-related stress and dementia are shown in Table 3.

Among CAIDE participants, higher levels of work-related stress were associated with

MCI (Model 2: OR, 1.38, 95% CI: 1.08–1.76), dementia (Model 2: OR: 1.53, 95% CI:

1.13-2.07) and Alzheimer's disease (Model 2: OR: 1.55, 95% CI: 1.19-2.36) at the first

re-examination (1998). Associations remained significant after basic adjustments (models

1) as well as extensive ones (models 2) (Table 3). Work-related stress was not associated

with a higher risk of any form of cognitive impairment or Alzheimer's disease between the first and the second re-examination (2005-2008).

Among the entire target population, including linked register diagnoses and deaths also for non-participants, midlife work-related stress was not significantly associated with dementia or Alzheimer's disease at the first follow-up or the second follow-up, even after adjusting for confounding factors.

Considering that some of the covariates might have different associations to the outcomes if they are measured at the follow-ups, we performed sensitivity analyses where we added available covariates from the corresponding follow-ups (first or second re-examination) that may have changed since baseline (BMI, systolic blood pressure, cardio/cerebrovascular conditions, smoking, cholesterol, hopelessness). Our results did not change. All analyses for the first re-examination remained significant, where work-related stress was associated with a higher risk for MCI, dementia and Alzheimer's disease in the first re-examination (all $p < 0.05$). The analyses for the second re-examination also remained non-significant after adding the additional covariates from the second re-examinations (all $p > 0.05$).

Discussion

The current study shows that higher levels of work-related stress in midlife are associated with an increased risk for MCI, dementia, and Alzheimer's disease later in life. Participants with higher work-related stress had a higher risk for MCI, dementia, and Alzheimer's disease at the first follow-up, approximately 21 years later. This association

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remained significant after controlling for several confounding factors. Higher work-related stress was not associated with dementia or Alzheimer's disease during the extended follow-up (approximately 28 years later) among CAIDE participants.

There may be several reasons for the time-specific association we found between midlife work-related stress and MCI, dementia and Alzheimer's disease at the first follow-up. One is selective mortality and selective participation. Survivors who attended the second follow-up may represent a more resilient sub-group less likely to develop dementia. Dementia among the oldest old (75+) is more heterogeneous than dementia among younger-old individuals, where risk and protective factors accumulated throughout the life-course affect the risk and thus, may dilute the effect of a single risk factor (here midlife stress) (Corrada, Berlau, & Kawas, 2012; von Gunten, Ebbing, Imhof, Giannakopoulos, & Kovari, 2010). Protective factors may delay the onset of dementia, but it is still unknown how far this effect can last. In our study, individuals with lower levels of midlife work-related stress were protected against cognitive impairment and dementia at young-old ages (1st follow-up, mean age 71 years) but not during the extended follow-up (mean age 78 years), suggesting that midlife stress may have a 'critical time window' concerning the effects on dementia onset.

We attempted to account for survival and non-participation bias in the sensitivity analyses (entire CAIDE population). The lack of association in these analyses may be partly, in addition to the aforementioned reasons, due to dementia diagnoses being under-reported in registers. More specifically, a recent analysis of the validity of dementia and Alzheimer's disease diagnoses in Finnish national registers demonstrated that prior to

1998 (the same year of the CAIDE first re-examination), the Hospital Discharge Register had low sensitivity and positive predictive values for dementia and Alzheimer's disease diagnoses. Sensitivity increased from 7.3% during the period 1972-1998 to 17.7% during 1998-2008 (Solomon et al., 2014). The positive predictive value also increased from 57.1% before 1998 to 84.6% after 1998 (Solomon et al., 2014). This is likely to have prevented us from finding the same associations between work-related stress and dementia when using data from the registers.

Previous longitudinal studies on stress and dementia showed that chronic perceived stress, low job control, low social support and frequent stress-related symptoms were independently associated with increased dementia risk (Andel et al., 2012; Crowe et al., 2007; Johansson et al., 2010; Wang et al., 2012). Similarly, low job control combined with low or high job demands increases dementia risk (Wang et al., 2012). To our knowledge, the current study is the first to show a specific effect of work-related stress in the form of constant hurry at work independently increases dementia/Alzheimer's disease risk. It was interesting to find that only time pressure, and not work demands, is associated with dementia/Alzheimer's risk. It has been reported that although from a scientific definition, stress does not equate time pressure, in more popular terms, when individuals subjectively indicate their source of stress, time pressure is the most common response, where one is stressed by not having sufficient time to carry out the tasks at hand (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). This perception of having time pressure elicits a physiological response that makes an individual aware of their heightened stress levels (Lupien et al., 2007). It is possible that job demands on the other hand, are interpreted and perceived as challenging tasks that require higher levels of

engagement and cognitive capacities. Indeed, previous studies have shown that higher work demands can also be protective for cognitive functioning (Andel et al., 2011; Nilsen et al., 2014). Our work adds to the previous literature by showing that it is not work demands per se, but rather the perceived time pressure component ('constant hurry') that increases the risk for dementia. For future investigations, it remains to be clarified whether demanding/complex jobs are also associated higher work-related stress and elevated dementia risk. As suggested by Andel and colleagues, those with highly complex jobs may still be at elevated dementia risk if also exposed to elevated work-related stress (Andel et al., 2012). It will be important for future studies to simultaneously measure both work-related stress and work complexity to determine the interactions and mediating factors between both constructs.

Chronic work-related stress might increase dementia risk through various physiological mechanisms such as elevations of the stress hormone cortisol. High cortisol levels modulate memory performance, primarily through crossing the blood-brain barrier and impacting the hippocampus. Healthy older adults with chronically elevated cortisol levels or self-reported chronic stress over a 20-year period were shown to have smaller hippocampal volume (Gianaros et al., 2007; Lupien et al., 1998). This evidence is relevant considering that the hippocampus is among the first brain regions to atrophy in Alzheimer's disease. Patients with Alzheimer's disease show high cortisol levels, which are associated with rapid cognitive decline and disease progression (Csernansky et al., 2006; Huang et al., 2009; Popp et al., 2009).

That associations between midlife work-related stress and dementia were maintained, even after controlling for important confounding factors indicates that stress may have more direct effects on the pathogenesis and development of cognitive impairment and Alzheimer's disease. Chronic stress also leads to simultaneous dysregulations of systems that accelerate the aging process, a model known as allostatic load, for which a score can be calculated (McEwen, 2007). This model encompasses cardiovascular, immune and metabolic dysregulations, which are also dementia risk factors. Higher levels of allostatic load are associated with diverse disease outcomes including declines in cognitive and physical functioning, and mortality (Juster et al., 2011; Seeman, McEwen, Rowe, & Singer, 2001). It will be important for future dementia studies to measure the allostatic load score combined with self-reported stress to assess whether this will provide a more powerful predictor of dementia risk.

Our study has several strengths including the long follow-up duration from midlife to later-life, the large population, extensive cognitive assessments, inclusion of analyses for both participants/survivors and non-participants/deceased, and controlling for many potential risk factors. Some limitations should also be noted. First, stress in later-life as well as stress outside work were not measured, so it is unknown whether midlife work-related stress independently increases dementia risk. Second, no information was available on job control, which is an important factor in the field of work-related stress (Seidler et al., 2004; Wang et al., 2012). Third, the portion of dementia diagnoses obtained from the national registers may have underestimated the prevalence of dementia. It is however noteworthy that the quality of national registers in Finland is relatively high according to international standards (Lahti, 2005; Solomon et al., 2014).

This study provides compelling evidence, for the first time showing that midlife work-related stress characterized by perceived constant hurry at work, is associated with an increased Alzheimer's disease and dementia risk in a large representative population.

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Figure 1. Flowchart representing the study population and examinations in the CAIDE study.

1st RE-EXAMINATION (1998)

Invited random sample N = 2000

| Participants N = 1449
Completed cognitive assessments N = 1409
(dementia N = 61) | Non-participants N = 591
(Incomplete cognitive assessments/
poor health/refused/died) |

2nd RE-EXAMINATION (2005-2008)

All eligible individuals N = 1426
Not eligible N = 574 (died, moved from region, unknown address)

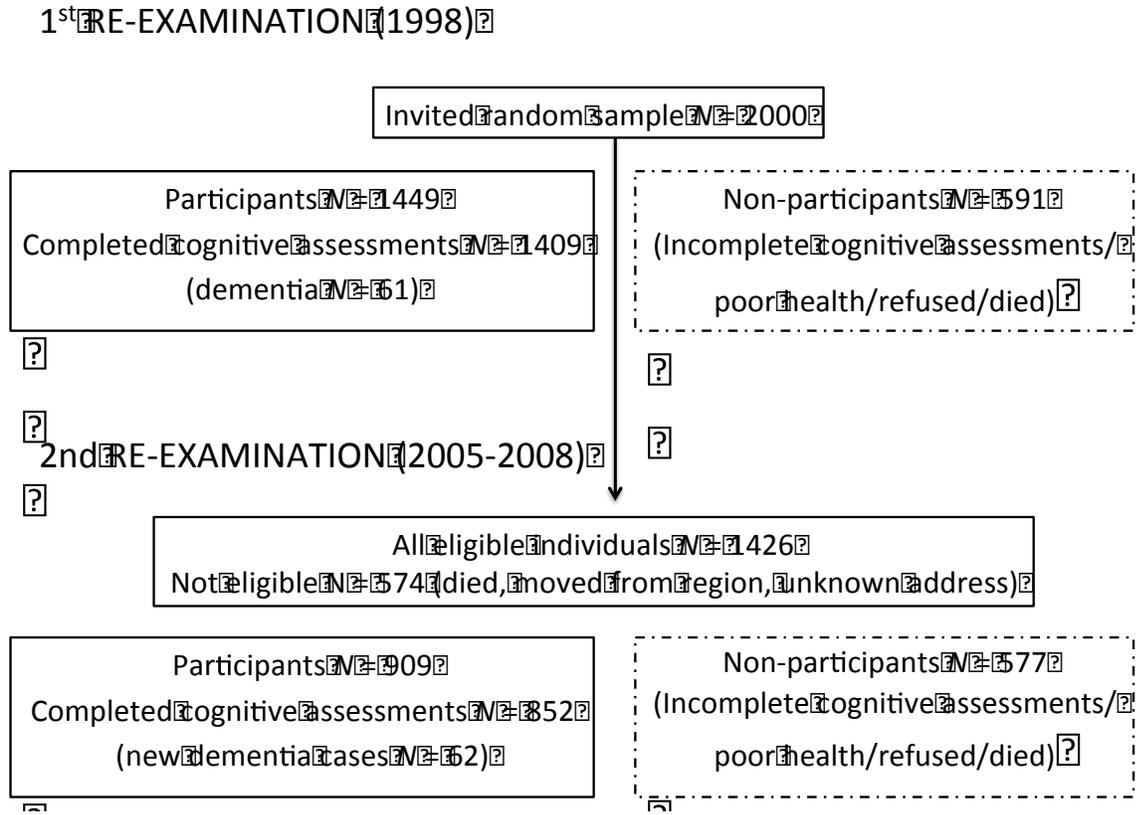| Participants N = 909
Completed cognitive assessments N = 852
(new dementia cases N = 62) | Non-participants N = 577
(Incomplete cognitive assessments/
poor health/refused/died) |

TABLE 1. Sociodemographic and clinical characteristics of the entire CAIDE target population.

Characteristics	Survivors/participants (n=1511)	Died/Non-participants (n=489)	p-value
Age at midlife	50.3 (6.0)	51.5 (5.9)	**<0.001**
Age at late-life[1]	78.8 (4.4)	78.9 (5.1)	N.S.
Sex			
Women	942 (62.3%)	308 (63.0%)	
Men	569 (37.7%)	181 (37.0%)	N.S.
Education (years)	8.6 (3.4)	7.4 (3.0)	**<0.001**
APOEε4 allele (non participants n = 29)			
Non-Carrier	889 (64.4%)	21 (72.4%)	
Carrier	491 (35.6%)	8 (27.6%)	N.S.
Work-related stress (range 1-5)	3.24 (1.10)	3.41 (1.17)	**0.006**
Midlife BMI	26.6 (3.8)	27.4 (4.4)	**<0.001**
Midlife systolic blood pressure (mm/Hg)	144.3 (20.0)	151.2 (21.4)	**<0.001**
Midlife cholesterol	6.8 (1.2)	7.0 (1.3)	**0.002**
Type of occupation			
White-collar	690 (47.3%)	154 (32.9%)	
Other	768 (52.7%)	314 (67.1%)	**<0.001**
Smoker			
No	859 (56.9%)	254 (51.9%)	
Yes	651 (43.1%)	235 (48.1%)	N.S
Living in a cohabitant relation			
No	304 (20.1%)	133 (27.2%)	
Yes	1,206 (79.9%)	356 (72.8%)	**0.001**
Midlife cardio/cerebrovascular / respiratory conditions			
No	1,457 (96.4%)	469 (95.9%)	

Yes	54 (3.6%)	20 (4.1%)	N.S.
Midlife hopelessness			
No	840 (57.38%)	198 (42.58%)	
Yes	624 (42.62%)	267 (57.42%)	**<0.001**
Midlife loneliness			
No	1,176 (78.93%)	351 (73.58%)	
Yes	314 (21.07%)	126 (26.42%)	**0.015**
Dementia (CAIDE and registers)			
No	1,239 (82.0%)	364 (74.4%)	
Yes	272 (18.0%)	125 (25.6%)	**<0.001**
Alzheimer's disease (CAIDE and registers)			
No	1,239 (85.1%)	364 (83.7%)	
Yes	216 (14.9%)	71 (16.3%)	N.S

Columnwise values are numbers (%) and χ^2 test was used unless otherwise indicated.
Values are means (SD) and independent samples T-test was used.
BMI = *Body mass index; MCI* = Mild Cognitive Impairment.
[1] Age at censoring (death or end of follow-up) or at diagnoses.

TABLE 2. The associations between work-related stress in midlife and the development of subsequent dementia.

Perceived work-related stress in midlife (1972-1987)	Diagnosis until 1st re-examination (1998) (OR and CI)		Diagnosis between 1st (1998) and 2nd re-examination (2005-2008) (RRR and CI)	
	Model 1	Model 2	Model 1	Model 2
Participants, dementia[a]				
1st re-examination: (N=1,343, dementia n=52)				
2nd re-examination: (N=1,343, dementia n=40)				
Work-related stress	**1.50 (1.15-1.96)**	**1.53 (1.13-2.07)**	0.98 (0.72-1.32)	0.97 (0.71-1.35)
Participants, Mild Cognitive Impairment[a]				
1st re-examination: (N=1,291, MCI n=75)				
2nd re-examination: (N=1,290, MCI n=122)				
Work-related stress	**1.25 (1.00-1.56)**	**1.38 (1.08-1.76)**	1.08 (0.91-1.29)	1.05 (0.88-1.27)
Participants, Alzheimer's disease (AD) [a]				
1st re-examination: (N=1,257, AD n=43)				
2nd re-examination: (N=1,267, AD n=37)				
Work-related stress	**1.50 (1.16-2.06)**	**1.55 (1.19-2.36)**	0.90 (0.65-1.23)	0.90 (0.64-1.26)
Entire target population, dementia [b]				
1st re-examination: (N=1,846, dementia n=92)				
2nd re-examination: (N=1,846, dementia n=356)				
	Diagnoses until the end of 1998		**Diagnoses until the end of 2008**	
Work-related stress	1.02 (0.85-1.23)	1.02 (0.84-1.24)	0.96 (0.87-1.05)	0.95 (0.86-1.04)
Entire target population, Alzheimer's disease [b]				
1st re-examination: (N=1,846, AD n=65)				
2nd re-examination: (N=1,846, AD n=265)				
Work-related stress	1.20 (0.97-1.49)	1.21 (0.95-1.53)	1.00 (0.90-1.12)	1.00 (0.90-1.13)

Note: numbers of dementia and Alzheimer's disease cases are presented for participants with available information for models 1.

[a] Logistic regression models. Model 1 adjusted for age, sex, education, APOE ε4 and follow-up time. Model 2 additionally adjusted for midlife BMI, respiratory, cardio/cerebrovascular and musculoskeletal conditions, systolic blood pressure, cholesterol, type of occupation, smoking, cohabitant status, hopelessness and loneliness

[b] Hazard regressions with Gompertz distributed baseline intensity. Model 1 adjusted for sex and education. Model 2 additionally adjusted for midlife BMI, respiratory,

cardio/cerebrovascular and musculoskeletal conditions, systolic blood pressure, cholesterol, type of occupation, smoking, cohabitant status, hopelessness and loneliness